PHARMACEUTICAL RESEARCH AND DEVELOPMENT: A KEY INFORMANT ASSESSMENT OF WHETHER AN “OPEN-SCIENCE” MODEL COULD IMPROVE CLINICAL RESEARCH IN TERMS OF QUALITY AND EFFICIENCY

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ABSTRACT

TIMOTHY KING: Pharmaceutical Research and Development: A Key Informant Assessment of Whether an “Open-Science” Model Could Improve Clinical Research in Terms of Quality and Efficiency
(Under the direction of John E. Paul)

The average cost to develop each new pharmaceutical drug is approximately $1 billion or more and takes 12-15 years from laboratory concept to an approved drug on the shelf at the local pharmacy. There is concern that the high cost and extended timelines required for pharmaceutical research and development (R&D) is not sustainable in the long term, as pharmaceutical companies question the value of investing $1 billion against an uncertain future revenue stream. The high cost of R&D contributes to the high cost of pharmacotherapies to consumers, where one recent estimate projects that annual global spending on pharmaceuticals will exceed $1.2 trillion by 2016.

Spending over $1 trillion on pharmaceuticals each year is a burden on global health resources. Therefore, reducing the cost of pharmaceuticals could have a tremendous impact on patients’ access to healthcare. A potential source of cost reduction is to improve efficiency in pharmaceutical R&D while protecting patient safety and maintaining or improving research quality. If savings in pharmaceutical R&D could be passed on to consumers, this would result in lower pharmaceutical prices and healthcare costs worldwide.
One concept proposed to improve R&D efficiency and quality is to make the process more transparent and collaborative where researchers, even those from competing pharmaceutical companies, could more freely share information on their research designs, processes and outcomes. This concept, “open-science” R&D (OSRD), differs from traditional R&D approaches that typically are more secretive and less collaborative.

To explore whether OSRD could be a viable and beneficial alternative to current pharmaceutical R&D practices, key informants from academia, industry, and regulatory agencies were interviewed using a qualitative, semi-structured questionnaire. While the key informants were concerned that for-profit pharmaceutical companies would not voluntarily embrace OSRD, the results also revealed that, 1) OSRD may be more efficient and therefore better in terms of R&D costs, 2) many OSRD-type activities are already in place, 3) more transparency is probably inevitable, and 4) senior leaders, including those in industry, are open to exploring opportunities for broad transparency and collaboration such as those envisioned in OSRD.
Dedicated to Kimberly, Bennett and Susanna
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Bill Andrews, Dennis Gillings, Pat King, Robert Millikan, Katherine Rowan, and David Sokal, who provided inspiration to seek solutions to the world’s biggest challenges; *maius opus moveo*.

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General support and encouragement of my friends and colleagues in Cohort Six of the DrPH program. It was my honor to begin and end this journey with you all.

And finally, the key informants who participated in the interviews, freely sharing their time and expertise.

To these people named and many more unnamed, my humble gratitude.

*In Memoriam:* Drs. Robert Millikan and John Vernon
PREFACE

The last 60 years of innovations in clinical research have not made the enterprise more efficient – actually the opposite. Analysis shows that while the number of drugs approved annually fluctuates to some degree, overall approvals have remained static while the financial resources required for research and development (R&D) have soared at a rate well beyond inflation.¹

In 2008, I was a Group Director at Quintiles, a large contract research organization (CRO), which provides financial, research, and sales support to the pharmaceutical industry. Founder and then CEO Dennis Gillings stated in internal communications that the cost of pharma R&D was unsustainable and that Quintiles needed to find ways to “conduct three clinical trials for the cost of two” (personal communication). Put another way, the industry needed to reduce the cost of R&D by 33%. He referred to Quintiles’ corporate goal to reduce pharma R&D costs as the “3 for 2” initiative, and charged me and my colleagues to propose innovations to the current pharma R&D process to improve efficiency (reduce time and costs) while maintaining if not improving process quality. This corporate goal did not necessarily refer to improving quality in terms of the safety and efficacy of approved drugs, but to improve the quality of the R&D process.

Many initiatives were proposed including Six-Sigma² reviews of and modifications to Quintiles’ business processes and upgrades to computer software
and information systems. However, I viewed these innovations, although helpful, as incremental and unlikely to have a substantial impact on R&D process quality and efficiency. I theorized that the lack of transparency and collaboration in drug development may be doing more harm than good to the pharma business. While secrecy is intended to protect proprietary information and business interests, it may make the R&D process so inefficient that the net result could be an overall negative impact on profitability and sustainability, not only to the bottom line for Quintiles but to the entire drug development industry. I therefore proposed that Quintiles explore ways to promote transparency and collaboration among our pharma customers as a means to improve R&D, and I have come to refer to this approach as open-science R&D (OSRD).

Moreover, to someone trained in population health, I felt that improving efficiency in pharma R&D could have a positive impact on global health by reducing the high cost of pharmacotherapies. Whether the inefficient processes in R&D can be significantly improved by OSRD is an issue much larger than the internal business processes of one CRO or pharma company, and therefore this research explores the viability of OSRD across the entire pharma industry.

It is important to note that throughout this paper the focus is pharmaceuticals, but any beneficial innovations for R&D arguably would have similar benefits for other medical R&D efforts including medical devices and diagnostics.
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>510-K</td>
<td>For FDA approval for new Medical Devices that are substantially equivalent to existing, approved devices</td>
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<tr>
<td>ACA</td>
<td>Affordable Care Act</td>
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<tr>
<td>ADME</td>
<td>Absorption, Distribution, Metabolism, and Excretion</td>
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<tr>
<td>AE</td>
<td>Adverse Event (in a clinical trial, a “side effect”)</td>
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<tr>
<td>CDC</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>CEO/CMO</td>
<td>Chief Executive/Chief Medical Officer</td>
</tr>
<tr>
<td>CER</td>
<td>Comparative Effectiveness Research</td>
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<tr>
<td>CMC</td>
<td>Chemistry, Manufacturing, and Control</td>
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<tr>
<td>CRO</td>
<td>Contract Research Organization</td>
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<td>CITI</td>
<td>Collaborative Institutional Training Initiative</td>
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<td>CTTI</td>
<td>Clinical Trials Transformation Initiative</td>
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<tr>
<td>DNDi</td>
<td>Drugs for Neglected Diseases Initiative</td>
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<tr>
<td>EMA</td>
<td>European Medicines Agency</td>
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<tr>
<td>FDA</td>
<td>United States Food and Drug Administration</td>
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<tr>
<td>FOI</td>
<td>Freedom of Information Act</td>
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<tr>
<td>IDE</td>
<td>Investigational Device Exemption (for FDA approval to begin human testing for candidate medical devices)</td>
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<tr>
<td>IND</td>
<td>Investigational New Drug (for FDA approval to begin human testing for candidate pharmacotherapies)</td>
</tr>
<tr>
<td>IP</td>
<td>Intellectual Property, such as the molecule that is patented</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
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<tr>
<td>iSAEC</td>
<td>International Serious Adverse Event Consortium</td>
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<td>KI</td>
<td>Key Informants</td>
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<td>Acronym</td>
<td>Full Form</td>
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<tr>
<td>NACDS</td>
<td>National Association of Chain Drug Stores</td>
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<tr>
<td>NDA</td>
<td>New Drug Application (for FDA approval of new pharmacotherapies)</td>
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<tr>
<td>NIH</td>
<td>National Institutes of Health</td>
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<tr>
<td>NTD</td>
<td>Neglected Tropical Diseases</td>
</tr>
<tr>
<td>OSRD</td>
<td>Open-Science Research and Development</td>
</tr>
<tr>
<td>pharma</td>
<td>The pharmaceutical industry and/or company</td>
</tr>
<tr>
<td>PhRMA</td>
<td>Pharmaceutical Research and Manufacturers of America</td>
</tr>
<tr>
<td>PHS</td>
<td>Public Health Service</td>
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<tr>
<td>PK/PD</td>
<td>Pharmacokinetics/Pharmacodynamics</td>
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<tr>
<td>PMA</td>
<td>Pre-Market Authorization (for FDA approval for new Medical Devices)</td>
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<tr>
<td>POC</td>
<td>Proof of Concept, usually a Phase II clinical trial</td>
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<tr>
<td>R&amp;D</td>
<td>Research and Development</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomized Clinical Trial</td>
</tr>
<tr>
<td>ROI</td>
<td>Return on Investment</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious Adverse Event</td>
</tr>
<tr>
<td>SG&amp;A</td>
<td>Selling, General, and Administrative Expenses</td>
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<tr>
<td>VP</td>
<td>Vice President</td>
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Chapter 1: Introduction

Problem Statement

The high cost of pharmaceuticals reduces patient access to needed therapies and places an enormous burden on healthcare worldwide, and therefore is a global population health issue.\(^3\)

Data suggest that per each new approved drug, pharmaceutical companies (pharma) must invest on average $1 billion or more over 12-15 years to proceed from laboratory concept to an approved drug on the shelf at the local pharmacy.\(^4,5\) Another analysis of costs for each new drug approved from 1997 – 2012 among the ten largest pharma companies estimated the costs at approximately $4 – 12 billion.\(^6\) Totaled across all drugs in development, the Pharmaceutical Research and Manufacturers of America (PhRMA), an industry-sponsored association, reports that 2010 R&D investments approached $67 billion.\(^7\) There is consensus that this business model is not sustainable in the long term,\(^1\) as investors question the value of investing $1 billion or more per approved drug when measured against a highly uncertain return on investment (ROI).

Pharmaceutical companies maintain that the high cost of R&D is a driver for the high cost to consumers of approved therapies. In Canada, for example, data from 2004 showed that the cost of pharmaceuticals exceeded the cost of physician
services.\textsuperscript{9} Recent reports estimate that the global expenditure for pharmaceuticals will exceed $1 trillion by 2014\textsuperscript{9} and $1.2 trillion by 2016.\textsuperscript{10}

Therefore, in theory, significant reductions in pharma R&D investments would result in lower costs to pharma per approved drug. Pharma companies could then reduce the amount they charge consumers without eroding profit margins. In other words, if pharma needed to invest less for R&D, they could charge less per prescription to recover their R&D expenditures while maintaining current profit margins. Most importantly, if potential savings were passed on to consumers so that pharmacotherapies are less expensive, this could result in greater access to needed therapies for all people.

**Proposals to Reduce Pharmaceutical Costs**

As a result, many efforts are proposed or underway to decrease or at least reduce the rate of increase in pharmaceutical costs. Initiatives or market forces that may have a substantial impact on the costs of drugs include:\textsuperscript{9}

- **“Patent Cliff”**: Many of the highest revenue generating pharmacotherapies are facing patent expiry by 2015, leading to increased production and demand for much less expensive generic drug options for over ten of the most profitable prescriptions.\textsuperscript{11} Note that generics tend to cost one-third of their brand name equivalents.\textsuperscript{12}

- **Biosimilars**: Recent rulings in the US and Europe are opening regulatory pathways to demonstrating that biosimilars are as safe and effective as
already approved biologic drugs, akin to generic drugs for small-molecule pharmaceuticals.\textsuperscript{13}

- **Comparative Effectiveness Research (CER):** Through CER data are analyzed to determine the most effective therapies for the cost. These data can then be used to guide patient, physician, and payer decision making.

- **Payer Reform:** Both public (Medicare/Medicaid in the US) and private insurance payers are organizing and exerting more pressure on pharmacotherapy pricing in terms of which approved drugs payers are willing to purchase, for which patients, and at what price.

- **Improving Pharmaceutical R&D:** The endeavor to make research better at determining the safety and effectiveness of potential therapies, while also more efficient and less expensive to conduct.

  On this last point, one possibility for improving pharma R&D in terms of quality and efficiency is creating more transparent and collaborative process. This concept is sometimes referred to as “Open-Science”, “Open-Source”, “Open Innovation”, or “Crowd-Sourcing”\textsuperscript{14,15} in drug discovery and development. For the remainder of this paper, the term open-science R&D (OSRD) is used to represent the broader concept of transparency and collaboration in pharma R&D which is the focus of this research.

  It is also important to note that throughout this paper pharmaceuticals, pharmacotherapies, and drugs are referenced, but any beneficial innovations for
R&D arguably would have similar benefits for other medical R&D efforts including medical devices and diagnostics.

**Current Drug Discovery and Development Process**

The first step assessing whether an OSRD approach could be beneficial in terms of R&D process quality and efficiency is to review the current drug discovery and development process. Most drugs are developed by private, for-profit pharmaceutical companies, although academic and/or government funded researchers also can have significant roles in the basic science and drug development process. Private in this case means not primarily supported by public (government) funding, but the companies may be either publically traded or privately held. These private businesses seek patents so that they own the drugs they are developing, and these patents can be on: 1) the molecular structure, 2) drug synthesis and manufacturing techniques, and, 3) “use” patents referring to the diseases or conditions the molecule is intended to treat. The patents are considered the intellectual property (IP) of each pharmaceutical company, which carefully protects its IP and works to keep it proprietary. In addition to protecting patented information, pharma companies tend to protect trade secrets – information that is not patentable but that pharma companies assume they should keep secret to protect their business interests. Examples of trade secrets include study protocols, data and results, and correspondence with regulatory agencies.

This secretive dynamic applies to the drug discovery process, where potential compounds are synthesized and tested in a laboratory. The goal of drug discovery is
to create and identify unique molecules that have certain properties that should, in theory, have a beneficial medicinal effect, without having properties known or suspected to cause an adverse event (AE), or negative side effect. When such compounds are identified, the discoverer may then seek to obtain patents as described above. If patents are granted, then the patent holder may proceed to the drug development stage and seek regulatory approval to sell the drug.

Drug development progresses through several stages (Figure 1), beginning with discovery and pre-clinical research that includes laboratory and animal testing for safety and also efficacy if possible. If the pre-clinical data are positive and compelling, a drug developer may then seek permission from a regulator such as the United States’ Food and Drug Administration (FDA) or the European Medicines Agency (EMA) to begin testing in human beings – the clinical development phase.
Figure 1. Drug discovery and development pathway

PhRMA, 2007.¹⁶

Traditional phases in clinical development include:

- **Phase I:** Several studies to demonstrate “proof of concept”, begin establishing drug pharmacokinetics (PK) and pharmacodynamics (PD), and monitor for significant risk of adverse events that would preclude future research. Phase I research involves relatively few patients or healthy volunteers, often less than 20-30 per study, and usually includes no inferential statistical testing.

- **Phase II:** Typically these are larger studies to establish minimally effective dose, maximum tolerated dose, and optimal dose or doses to carry forward into Phase III testing.
• **Phase III:** These are the largest studies to determine safety and efficacy with statistical significance. Phase III research often requires two large, well-controlled, randomized trials (RCT) for market approval, can involve hundreds if not thousands of patients, and cost tens if not hundreds of millions of dollars to conduct.

• **Phase IV:** Phase IV studies are also called post-marketing research and are conducted after the drug has been approved. Sometimes required by regulators after granting a contingent approval, Phase IV research often seeks to clarify the safety and efficacy of the approved drug in “real world” settings, meaning where patient selection and drug compliance is not tightly controlled as in the RCT(s) required in pre-approval research.

  Patents for pharmaceuticals typically are granted for 20 years, and assuming it requires on average 12-15 years and $1 billion to test the compound and receive regulatory approval, then a pharma company perhaps has only five years to recoup the bulk of the R&D investment, much less make a profit, some of which may then then spent on R&D for new drug candidates.

**Transparency and Collaboration in Drug Development**

Under the current business model, drug developers seek to keep as much information as possible about their drug candidate proprietary and protect their IP. Therefore, research methodologies and results, particularly any data that do not
support the business goal of gaining drug approval and support marketing, largely remain hidden from public scrutiny.

The Collaborative Institutional Training Initiative (CITI) is an independent group created to train investigators on ethical conduct in clinical research. The CITI training is required for many scientists involved in research funded by either the Public Health Service (PHS) or the National Institutes of Health (NIH), as well as some industry-funded research regulated by the FDA. To CITI, the lack of transparency in research has a negative impact on the advancement of science and therefore on patients:

“[Pharma companies] may seek to restrict publication, citing protection of proprietary information, in order to avoid advancing the work of competitors. They may conceal negative study findings by maintaining control of publication, or avoid disclosing adverse events and side effects to the public (though these are disclosed to the FDA). Restricted or partial publication increases the cost of clinical progress and can jeopardize the health of future study subjects and future patients. It also impedes or disrupts the work of other scientists whose work would otherwise improve, build on or impeach prior investigations.”

Expanding on the concerns expressed by CITI, the lack of communication, collaboration and transparency in the current paradigm of pharma R&D may contribute to a variety of problems including:

1. **Sub-optimal research design and analysis**: As pharmaceutical company researchers do not freely share study design and analysis methodologies outside their organizations, and also because confidentiality inhibits regulators such as the FDA or EMA from directly sharing best practices
between drug developers, the broader community of researchers do not benefit from the knowledge of others.

2. **Redundant research**: Different pharma companies that are developing similar drugs do not share results, particularly negative results which is akin to the issue of negative publication bias, and this can propel drug candidates much further down the development pathway before failing than they might have gone otherwise. Redundant and unnecessary clinical studies drive up the costs of failed drug candidates, which must then be recovered in the pricing of approved drugs.

3. **Trust**: A Harris Interactive poll of approximately 1700 people in the US in 2006 found that more than 85 percent of American adults believe that the FDA and pharma companies have at least “a fair amount” of responsibility for “ensuring drug safety”. However, only a fraction of those polled believed that the FDA (45 percent) or pharma companies (27 percent) could be trusted with drug safety. Moreover, only 14 percent of participants were “very confident” that pharma companies would eventually release data on drug safety, regardless of whether the data were positive or negative. This situation has led researchers to propose that greater transparency in pharma R&D could restore trust in the pharma industry and the therapies it produces.

In theory, problems #1 and #2 described above would tend to render pharma R&D less efficient and thereby increase the cost of developing drugs. Problem #3 might compel pharma companies to invest more resources in advertising and
marketing than might otherwise be required to simply advertise drugs to providers and patients. Using data from 2004, Gagnon and Lexchin estimate that pharma companies each year spend twice as much on advertising and marketing as R&D, even when including additional public funding for R&D such as from the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention (CDC).²² The high cost of R&D, and even higher cost of advertising and marketing, is ultimately costs passed on to consumers. High drug costs limit access to consumers, and thus the cost of drug R&D is a population health issue.³
Chapter 2: Review of the Literature

The literature review for this research included three components, namely:

1. Topic 1: The costs of pharma R&D under the current business model, to assess widely quoted estimates of $1 billion or more per each new approved drug;

2. Topic 2: The relative cost of pharma R&D when compared with total cost of a prescription to the consumer; and

3. Topic 3: The concept of open-source, crowd-sourcing, open-innovation, or open-science in pharma R&D.

**Literature Review Methods**

**Search Strategy**

Initially, a search was done of PubMed and Web of Knowledge for peer-reviewed articles published in English from 1980 to present using the following keywords:

- *pharmaceutical and drug development*
- *pharmaceutical and drug research*
- *medical device and diagnostic development and research*
- *costs and expenditures*
• *open-source, open-science, and crowd-sourcing.*

These keywords were also used for a “grey” literature search of Google and Google Scholar to find reports, non-peer reviewed articles, presentations, editorials, and opinion pieces. Finally, the reference lists of potentially relevant articles were also reviewed to identify additional articles.

Abstracts or summaries (when available) of potential articles were reviewed and included if they:

1) contained directly collected or imputed data on pharmaceutical development costs;
2) were in English; and
3) were published from 1980 to 2011, although some included data prior to 1980.

Articles were excluded if they simply repeated data or analysis from other identified articles or were commentaries on pharmaceutical development costs, but presented no original data or analyses.

It should be noted that a large portion of the information summarized here was gathered from “grey” literature, meaning newspaper, magazine, and web-based articles and editorials. This heavy weighting on the grey literature is due to two main factors:

1) For searches #1 and #2 above, just as the pharma industry is not forthcoming with general information about its pharma R&D efforts, it is also guarded
concerning information on the cost of R&D. Therefore, there are little data, particularly in peer-reviewed journals, that address the first two questions described above.

2) For search #3 above, the concept of open-source in computer development only began gaining momentum in the 1990s, and the theoretical or practical application of these concepts to pharma R&D is less than ten years old. Therefore, little has been published on the subject in any format, professional journals or grey literature.

**Topic 1: Cost of Pharmaceutical R&D**

Before it can be determined whether an OSRD approach could reduce pharmaceutical R&D costs, the first task is to understand the cost of developing drugs under the current business model. Costs and timelines frequently referenced in editorials indicate that the average drug takes 12-15 years and costs $1 billion or more to progress from the research laboratory to an approved drug.

Searches were conducted in PubMed, Web of Knowledge, and Google Scholar, generating the following number of potential references:

- PubMed = 1 272
- Web of Knowledge = 4 708
- Google Scholar = “about 74 000”
The original number of potential references from Web of Knowledge and Google Scholar were too large to review completely. A cursory review showed that the initially proposed search terms were capturing many different types of medical therapy costs outside the cost of developing new therapies, including the price of drugs for hospital formularies, Medicare reimbursements, etc. Therefore, for Web of Knowledge the search terms were modified to attempt to make them more selective: “pharmaceutical research and development costs”. This modification reduced the potential references from Web of Knowledge to 753, which then were filtered on “articles” to remove reviews (183) and editorials (28). Ultimately, the search resulted in 439 potential articles, which were reviewed for relevance by title.

For Google Scholar, the search term was revised to match Web of Knowledge, and the first 500 reference titles were then reviewed. This is admittedly an incomplete process, relying on Google’s proprietary and unknown algorithm to prioritize articles starting with the “closest” matches as determined by Google. However, the Google search did not reveal articles that were not already identified via Web of Knowledge, and therefore the risk of overlooking potential studies on R&D costs is small.

Concurrently, Morgan et al.⁴ was used as a benchmark, where the authors recently completed a systematic review based on 13 articles published from 1979 to 2010 (data from 1963 to 2010). The searches described above confirmed these 13 references and all but one book chapter that could not be retrieved²³ were reviewed directly.
In addition to these 13 articles, two additional references were identified and included in this literature review (Nunn 2006\textsuperscript{24} and Gilbert 2003\textsuperscript{25}). If either reference were originally found by Morgan et al., they presumably were intentionally excluded. First, Nunn\textsuperscript{24} provided estimates for imaging agents, outside the scope of the Morgan et al. systematic review of pharmacotherapies. Gilbert et al.\textsuperscript{25} was a private report from a consulting company and the data sources and methods were not revealed, which may have made it incompatible with criteria for inclusion in the Morgan et al. review.

In addition to these articles reporting cost estimates for pharmaceutical R&D, a number of editorials were noted, many stating concerns about the methodology and conclusions reported by the referenced articles. The main points of the editorials are summarized later in this literature review.

In the 15 articles included in this review, four different methodologies were used to estimate the cost to develop a drug. Morgan \textit{et al.} described them as follows:

- Method 1: Retrospective cost accounting with project-level data;

- Method 2: Retrospective econometric analysis with industry- or firm-level data;

- Method 3: Retrospective cost accounting with industry-level data; or

- Method 4: Prospective estimates of the cost of developing a hypothetical drug product.
Method 1\textsuperscript{24,26,27,28,29,30,31,32,33} attempted to retrospectively gather data on the cost of each task billed to the development of a drug, such as the cost to conduct each study (IRB fees, investigator physician fees, etc.), and the cost to produce the drug and placebo needed for the various studies. By far the vast majority of studies cited used this methodology, and most analyses for Method 1 were conducted by the same core group of researchers\textsuperscript{27,28,29,30,31,32} or by others explicitly seeking to replicate their methods.\textsuperscript{24,33}

Method 2\textsuperscript{34,35} differs in that the technique is to a) estimate R&D costs, b) create a model showing how many drugs are being developed at what stage (pre-clinical/non-human research, clinical, presumably including Phase I, II and III, etc.), and then c) use the model to estimate the incremental cost to develop an additional drug.

Method 3\textsuperscript{36} attempted to account for total costs over a specified period, but collected at the industry-wide level, meaning the costs for developing all drugs over five years (numerator). These industry-wide costs were then divided by estimates for the number of drugs developed during that same period (denominator), resulting in an estimate of the average cost of developing each drug in that period.

Finally, Method 4\textsuperscript{37} is similar to Method 1, except that the data were collected prospectively, using projected estimates of costs for each major task in the hypothetical development of a drug for tuberculosis. In both Methods 1 and 4, the stated goal was to capture the average cost to develop a single drug at a single pharmaceutical company.
Gilbert et al.\textsuperscript{25} did not describe their methods or original source data but are included here for completeness.

A common feature of the four methods is that most researchers attempted to account for the cost of drugs that failed to reach the market, meaning that the costs to develop drugs that failed to be approved must be covered by the drugs that succeed. It is important to note that, regardless of method, most studies relied on confidential data supplied by industry, therefore making it impossible for any researcher to independently verify the ultimate source of the original data much less its accuracy.

Table 1 summarizes results from the articles retrieved, stratified by the stage of development.
Table 1: Table of pharmaceutical development costs, with reference to data source and year, in $ millions

<table>
<thead>
<tr>
<th>Development Phase</th>
<th>Cost in $ millions (Year)</th>
</tr>
</thead>
</table>
| Discovery         | $600 (2003)\textsuperscript{25}  
$674 (2010)\textsuperscript{33} |
| Pre-Clinical      | $80 (2003)\textsuperscript{25}  
$89 (1963-75)\textsuperscript{b}  
$150 (2010)\textsuperscript{33}  
$264 (1970-82)\textsuperscript{27,c}  
$381 (2000)\textsuperscript{34}  
$415 (1983-94)\textsuperscript{30,c}  
$482 (1990-2003)\textsuperscript{32,c} |
| Phase I           | $100 (2003)\textsuperscript{25}  
$273 (2010)\textsuperscript{33} |
| Phase II          | $300 (2003)\textsuperscript{25}  
$319 (2010)\textsuperscript{33} |
| Phase III         | $73 (1963-75)\textsuperscript{b,c,d}  
$314 (2010)\textsuperscript{33}  
$487 (2000)\textsuperscript{34,d}  
$500 (2003)\textsuperscript{25}  
$578 (1983-94)\textsuperscript{30,c,d}  
$965 (1990-2003)\textsuperscript{32,c,d} |
| Marketing         | $48 (2010)\textsuperscript{33}  
$100 (2003)\textsuperscript{25} |
| Summary           | $753 - 1,778 |

\textsuperscript{a} Cumulative through NDA  
\textsuperscript{b} Hansen – as reported using data from Morgan et al. (2011)  
\textsuperscript{c} Morgan et al. (2011), capitalized into 2009 USD  
\textsuperscript{d} Phase I, II, and III Clinical costs combined
Overall, almost all data reported in Table 1 were for pharmaceutical development. No articles were found for medical devices, and only one article estimated R&D costs for medical diagnostics ($135 million). Drug development costs varied tremendously over a time span of 40 or more years, with the low and high-estimate differing by approximately $1 billion (adjusted for inflation at least through the year 2000). Therefore, inflation did not account for the large variance in R&D cost estimates.

Two articles sought to delineate costs by therapeutic areas such as cardiovascular, infectious disease, or oncology drugs. DiMasi et al.\textsuperscript{31}, using retrospective cost accounting (Method 1), expanded upon the general results reported in their 2003 research\textsuperscript{30} with a breakout of clinical costs for the therapeutic categories of central nervous system (CNS), anti-infectives, cardiovascular, and analgesics. They reported a range in clinical costs $464 to $609 million with anti-infectives being the most expensive to develop. Adams and Brantner\textsuperscript{38} used econometric modeling (Method 2) and delineated costs into several additional therapeutic categories, and reported that oncology, CNS, and pulmonary drugs were the most expensive to develop at over $1 billion each (2000 capitalized, clinical trial costs only, not overall R&D expenses). Table 2 provides a comparison of the two articles’ main results, adjusting for inflation through the year 2000.
<table>
<thead>
<tr>
<th>Category</th>
<th>DiMasi et al(^{28}) $ millions</th>
<th>Adams &amp; Brantner(^{38}) $ millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>-</td>
<td>$906</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>$111</td>
<td>$887</td>
</tr>
<tr>
<td>Dermatological</td>
<td>-</td>
<td>$677</td>
</tr>
<tr>
<td>Genitourinary</td>
<td>-</td>
<td>$635</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>$180(^{a})</td>
<td>$540</td>
</tr>
<tr>
<td>Cancer</td>
<td>-</td>
<td>$1,042</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>-</td>
<td>$946</td>
</tr>
<tr>
<td>Neurological</td>
<td>$100</td>
<td>$1,016</td>
</tr>
<tr>
<td>Anti-parasitic</td>
<td>-</td>
<td>$454</td>
</tr>
<tr>
<td>Respiratory</td>
<td>-</td>
<td>$1,134</td>
</tr>
<tr>
<td>Sensory(^{b})</td>
<td>-</td>
<td>$648</td>
</tr>
<tr>
<td>Analgesic</td>
<td>$114</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^{a}\) General Anti-infectives, where HIV/AIDS is a sub-group

\(^{b}\) Sensory drugs are not defined by the authors, but are assumed to eye and/or ear drugs to treat conditions such as glaucoma and tinnitus
In reviewing Table 2, only three subgroups have head-to-head comparisons, cardiovascular, HIV/AIDS, and neurological, and the costs differences ranged from three fold (HIV/AIDS) to ten-fold (neurological). These wide differences render consensus impossible. In other words, there are no agreed trends in R&D costs differences depending on the therapeutic area or diseases researched.

**Summary of Costs of Pharmaceutical R&D**

There is general consensus that the average drug currently requires $1 billion or more and 12-15 years to gain approval. The true cost to develop drugs is important, as the high cost of R&D is used to partially justify the high cost of pharmacotherapies to consumers. With only 20 years of patent protection, pharmaceutical developers have only a few years remaining of patent life to recover development costs much less to make a profit to fund on-going and future R&D efforts.

The articles summarized suggest that pharma R&D costs have risen dramatically since the 1960s, even when costs are adjusted for inflation. This rise in R&D costs is largely attributed to more drug candidates failing in later-stage trials, the higher cost of capital, and increased regulatory scrutiny requiring more, larger, and longer studies before a drug can be approved. This trend (rising R&D costs as the numerator) combined with a static or lower number of drugs being approved (denominator) results in substantially higher R&D costs per drug marketed. While there are reported differences in R&D costs depending upon the kind of diseases
treated or the type of company conducting the research (large pharma versus small biotech), there are far too few data to substantiate any conclusions.

Concerns remain whether the data reported on R&D costs are accurate. Only one of the four methods has been repeated to any great extent, and primarily by the same core group of researchers. Regardless of the methodology used to estimate the R&D costs, two primary trends emerge:

1. Despite the billions of dollars spent annually to develop hundreds of different pharmaceuticals, very few data are published on where and how these funds are used, and:

2. For the little amount of data published, the original sources are usually unnamed and unverifiable.

Therefore, while the conclusion that $1 billion and 12-15 years may or may not be substantively true, verified data to support this estimate are thin. Overall, information for pharmaceutical R&D costs is scarce; costs for devices and diagnostics is virtually nonexistent.

The methods used to estimate the cost of pharmaceutical development are imprecise. These methods have been challenged, usually because the source data come from unnamed pharmaceutical companies, who presumably have a strong interest in maximizing R&D costs estimates in order to justify high product costs. Another criticism is that none of the four cost estimation methods account for government funding for R&D, such as through the NIH, tax incentives or other
rebates that pharma companies sometimes receive. Overall, regardless of the cost estimation methodologies, most assume that any biases would tend to overestimate costs.

In conclusion, research on the cost of pharmaceutical development is criticized for many of the same reasons that R&D itself is attacked; that is, a lack of transparency coupled with a presumed bias towards skewing data in favor of maximizing profits and not patient benefit. The pharma industry can only address these concerns by improving transparency and allowing open access to independent parties to collect, analyze, and report R&D costs.

**Topic 2: R&D Costs and the Overall Cost of Marketed Pharmaceuticals to Consumers**

Few estimates exist on the cost of R&D versus to total cost of a drug to consumers. The estimates also tend to be highly variable, as pharmaceutical companies are guarded about their spending practices. Figure 2 below, reproduced from the National Association of Chain Drug Stores (NACDS), therefore must be interpreted cautiously given the uncertainty of the actual costs of pharma R&D.
Figure 2: Average revenue from each prescription required to cover the costs of R&D, manufacturing, distribution, marketing, etc.

From this figure a table was produced in order to calculate percentages (Table 3).
Table 3. Itemized costs contributing to the overall cost or a prescription from a retail pharmacy, based on NCADS estimates in Figure 2

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost ($)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer Cost of Materials</td>
<td>17.87</td>
<td>22.2</td>
</tr>
<tr>
<td>Manufacturer SG&amp;A</td>
<td>19.57</td>
<td>24.3</td>
</tr>
<tr>
<td>Manufacturer R&amp;D</td>
<td>11.95</td>
<td>14.8</td>
</tr>
<tr>
<td>Manufacturer Taxes</td>
<td>5.40</td>
<td>6.7</td>
</tr>
<tr>
<td>Manufacturer Total Profit</td>
<td>9.92</td>
<td>12.3</td>
</tr>
<tr>
<td><strong>Manufacturer Sub-total</strong></td>
<td><strong>64.71</strong></td>
<td><strong>80.4</strong></td>
</tr>
<tr>
<td>Wholesaler Operating Costs</td>
<td>0.62</td>
<td>0.8</td>
</tr>
<tr>
<td>Wholesaler Taxes</td>
<td>0.39</td>
<td>0.5</td>
</tr>
<tr>
<td>Wholesaler Net Profit</td>
<td>0.71</td>
<td>0.9</td>
</tr>
<tr>
<td><strong>Wholesaler Sub-total</strong></td>
<td><strong>1.72</strong></td>
<td><strong>2.1</strong></td>
</tr>
<tr>
<td>Retail Operating Costs</td>
<td>11.34</td>
<td>14.1</td>
</tr>
<tr>
<td>Retail Taxes</td>
<td>1.67</td>
<td>2.1</td>
</tr>
<tr>
<td>Retail Net Profit</td>
<td>1.09</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Retail Sub-total</strong></td>
<td><strong>14.10</strong></td>
<td><strong>17.5</strong></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>$80.53</strong></td>
<td><strong>100.0%</strong></td>
</tr>
</tbody>
</table>

% of R&D to manufacturer's costs 18.5%

The NACDS estimates that the average prescription in 2010 cost $80.53, which was then divided into several categories such as cost of materials, R&D, taxes, etc. This figure shows that R&D costs equal $11.95, or 14.8% of the total cost to the drug developer when the $11.95 is divided by the $80.53 total. Using the $64.71 estimate of the total share of a prescription cost that goes to the pharma company, then the percentage of R&D to a pharma company’s costs is $11.95 ÷ 64.71, or 18.5%. Other items that have a substantial impact on consumer drug costs include the cost of the raw materials (22.2%), selling, general, and administrative expenses (SG&A) (24.3%) and also profits (12.3%).
Other research in the grey literature suggests that the cost of the raw materials is much less (<1%)\textsuperscript{40} and state, but offer no data, that the proportion of R&D costs to the cost to consumer is much higher. It is important to note that the profits and SG&A are generated three times to account for the 1) manufacturer (drug company), 2) wholesaler (eg. McKesson, Cardinal, etc.)\textsuperscript{41}, and 3) retailer (local pharmacies). Based on these scant data, reducing R&D costs by as much as 50% would therefore only reduce the cost to consumer by 7.5%, which would reduce the NACDS estimated average cost of a prescription from $80.53 to $74.49 without requiring pharma to reduce profits. Overall, given estimates of spending for pharmacotherapies reaching $1.2 trillion by 2016\textsuperscript{10} a 7.5% reduction would equate to $90 billion in savings that could in theory be passed on to consumers each year.

**Topic 3: What is Open-Source Pharmaceutical R&D?**

There have been proposals for open-source drug discovery\textsuperscript{33,42,43} where development of potential drug candidates would progress in a completely open-source fashion, akin to open-source software development where the source code is not protected by patent. An example of open-source computer software development is a free and non-patented computer operating system called Linux\textsuperscript{44} comparable to computer operating systems that are patented and must be purchased such as Microsoft Windows™ and Apple OS™. Other terms referenced in the grey literature include “open innovation”, “crowd-sourcing” and “open-science”. In a completely open-source drug discovery model, researchers would have full access to all data on a potential molecule or compound, including patented or
normally patentable information such as its chemical structure and manufacturing techniques.

The open-source drug discovery model is built upon two assumptions that would hinder its utility for broader pharma R&D, namely:

1. Open-source drug discovery assumes that the model would be used only for unprofitable diseases where there is likely to be little or no commercial interests (e.g. neglected tropical diseases (NTD), “orphan” diseases); 45

2. Researchers pursuing open-source drug discovery into full clinical development would tend to be volunteers 46 or perhaps supported by grants or government funding. 42

This model proposes that, after potential drug candidates are found during the drug discovery stage, then clinical development might then be conducted, with no pharmaceutical company funding, by a decentralized community of self-interested and self-funded scholars. Open-source drug discovery proponents acknowledge this approach might be relevant to only a small number of compounds targeted for NTDs, and therefore only benefit a relatively small number of people from a global population health perspective, albeit among the most underserved.

The concept of open-source in the drug discovery stage is starting to be explored at large pharmaceutical companies and references to this can be found in the press such as this quote from the Wall Street Journal in 2011:
“Scientists also had to keep their work secret, exploring new medicines without insight from outsiders. But companies can’t keep a tight leash on their researchers if they expect to capitalize on the deepening understanding of how diseases happen, contends the chief executive of Sanofi SA, Christopher Viehbacher.” 47

Although not stated explicitly, this comment may only have referenced the basic science and drug discovery stage in the laboratory, as opposed to the clinical development stage in humans. However, a more recent quote from Christopher Viehbacher as part of a press release from the CEO Roundtable on Cancer is clearly directed at the full scope of pharma R&D:

“Broadly sharing existing clinical trial data for the benefit of all researchers can be a key driver in speeding up cancer research efforts, encouraging innovation, and honoring those patients who have participated in clinical trials as well as those future patients who deserve our very best collective efforts in discovering new and better therapies.” 48

In addition, a 30 January 2012 press release from the Drugs for Neglected Diseases initiative (DNDi), announced that 11 large pharmaceutical companies (Table 4) are co-investing $785 million to support collaborative R&D efforts:

“In the largest coordinated effort to date to combat NTDs, the group announced… that they would… share expertise and compounds to accelerate research and development of new drugs… Partners also… pledged new levels of collaborative effort and tracking of progress.” 49

These quotes from Sanofi and the DNDi are examples of large pharma companies endorsing the sharing of information and know-how with a goal of improving the R&D process.

Until recently there was little or no literature on the concept of open-source in the clinical development stage and/or on applying the concept to common diseases.
However, in September 2012, a consortium of ten large pharmaceutical companies (Table 4) created a not-for-profit, named TransCelerate Biopharma, to collaborate and share information:

“with the end goals of improving the quality of clinical studies and bringing new medicines to patients faster. Through participation in TransCelerate, each of the ten founding companies will combine financial and other resources, including personnel, to solve industry-wide challenges in a collaborative environment.”

Garry Neil, then interim CEO of TransCelerate stated,

"There is widespread alignment among the heads of R&D at major pharmaceutical companies that there is a critical need to substantially increase the number of innovative new medicines, while eliminating inefficiencies that drive up R&D costs… Our mission at TransCelerate BioPharma is to work together across the global research and development community and share research and solutions that will simplify and accelerate the delivery of exciting new medicines for patients."

TransCelerate and its academic partners intend to begin with five initiatives for collaboration which involve sharing information they deem to be “pre-competitive”. Pre-competitive appears to describe information that has traditionally been considered proprietary or “trade secrets” but not necessarily protected by patent.

The five initiatives are:

1. Creating a shared interface for investigator site portals, meaning web-sites that allow physicians and their staff who are participating in clinical trials to share information about their study(ies);

2. Mutually recognizing study site qualification and training, to avoid a current problem where if a site such as a doctor’s office is working on five different studies with five different sponsoring pharmaceutical companies, site staff
might have to complete some of the same qualification procedures and 
training five times;

3. Developing risk-based monitoring approaches and standards;

4. Further developing clinical data standards; and

5. Establishing a comparator drug model, where in many studies a potential new 
drug under investigation must be studied by comparing its safety and efficacy 
to that of an already approved drug.

TransCelerate is an unparalleled initiative where pharmaceutical companies 
are seeking to collaborate and share information in a way that would benefit all drug 
development, not just NTD. However, open-science R&D, as proposed below, goes 
farther than TransCelerate in that it contemplates the sharing of “competitive” 
information as well, e.g., protocols, study data, and regulatory interactions.
Table 4: Large pharmaceutical companies participating in the DNDi or TransCelerate as of 10 February 2012

<table>
<thead>
<tr>
<th>DNDi&lt;sup&gt;a&lt;/sup&gt;</th>
<th>TransCelerate&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>AbbVie (Abbott)</td>
<td>AbbVie (Abbott)</td>
</tr>
<tr>
<td>Celgene</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>Eisai</td>
<td>Boehringer Ingelheim</td>
</tr>
<tr>
<td>Genzyme</td>
<td>Bristol-Myers Squibb</td>
</tr>
<tr>
<td>Gilead</td>
<td>GSK</td>
</tr>
<tr>
<td>GNF Novartis</td>
<td>Johnson &amp; Johnson</td>
</tr>
<tr>
<td>GSK</td>
<td>Lilly</td>
</tr>
<tr>
<td>Merck</td>
<td>Pfizer</td>
</tr>
<tr>
<td>Pfizer</td>
<td>Roche</td>
</tr>
<tr>
<td>Sanofi</td>
<td>Sanofi</td>
</tr>
<tr>
<td>Vertex</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> from [www.dndi.org](http://www.dndi.org)

<sup>b</sup> from [www.transceleratebiopharmainc.com](http://www.transceleratebiopharmainc.com)

*bold* denotes participants in both efforts
Chapter 3: Conceptual Model and Research Questions

Drug Development: Conceptual Model

Pharmaceutical R&D follows the concept of the Scientific Method, encompassing the following four major components (Figure 3):

Figure 3: Components of the scientific method

The essential framework of the scientific method as shown in Figure 3 includes:

- Observation leading to a hypothesis, then to experiments, data gathering, analysis, and finally results that accept, partially accept, or reject the hypothesis. To this framework important additions have been made, including the concepts of transparency and reproducibility, perhaps dating back nearly 1000 years when scientist Roger Bacon “conducted his experiments in precise detail, perhaps with the idea that others could reproduce and independently test his results.” 51
Transparency, independent verification, and reproducibility are not widely practiced in for-profit pharma R&D, and therefore the current R&D process is in stark contrast to best practices in scientific research. As a result, the concept that optimal research should be transparent, reproducible, and conducted among the global community of scholars generally is not supported in for-profit medical research.

**Proposed Open-Science Research and Development Paradigm**

An open-science R&D (OSRD) paradigm as proposed in this research is not true “open-source” as understood by computer software developers and open-source drug discovery proponents. In a completely open-source R&D model, even patented information would be widely shared, including the molecular structure and means of synthesis.

Importantly, in the proposed open-science paradigm for pharma R&D, it is assumed that the discoverer and developer of the compound would still hold and keep proprietary any patent or patents, would fund R&D, and therefore could sell the drug or technology and seek profits if approved for marketing and distribution.

The reasons for maintaining a patent-based, for-profit model are two-fold:

1. To maintain profitability for developers in order to allay concerns that substantial profit erosion would undermine funding for future R&D, thereby reducing innovation in medical research.

2. To modify the current open-source R&D paradigm to make it applicable for all pharmaceutical R&D, rather than only NTDs and orphan diseases where
there is typically much less interest and investment from pharma. Therefore, an open-science process could have a much larger impact on global population health in both the developed and less developed world.

The proposed open-science model for pharma R&D would not be completely open-source as the source (molecular structure and synthesis) would still be patent protected and proprietary. However, the process or “science” of developing a molecule would be open and transparent, hence the proposed label, Open-Science Research and Development (OSRD).

The proposed OSRD process seeks to combine the concept of transparency and collaboration that is intertwined with the scientific method with the pharma R&D process. The underlying assumption is that the lack of transparency and collaboration in R&D reduces quality and efficiency, perhaps to the point of being financially negative, and that the efficiency and quality gained by an OSRD process may overcome any loss of competitive advantage that proprietary R&D is intended to protect. In short, the question is whether it is possible that more transparency and collaboration in for-profit pharma R&D could, under certain circumstances, be advantageous to patients as well as profitable to the pharma industry.

To understand what information would be made transparent in an OSRD process, first consider what is and is not open or shared in the current R&D model. During pharmaceutical discovery and development, the following information is kept proprietary as much as possible (Table 5):
Table 5: Information typically patented and/or kept proprietary under the current pharmaceutical R&D paradigm

- Molecular/Chemical Structure
- Synthesis and Manufacturing Processes
- Discovery process data such as *in vitro* laboratory testing (anti-viral activity, molecular binding, up and down-regulation of genes, computer modeling, etc.)
- Pre-clinical and Clinical Development Plans including Study Protocols
- Pre-clinical research (study designs, raw data, analysis)
- Targeted Product Profiles, marketing research
  - Animal toxicity
  - Animal efficacy models when possible
  - Mechanism of Action
- Clinical research (study designs, raw data, analysis)
  - Phase I (First-in-human, Clinical Pharmacology, etc.)
  - Phase II (Dose-finding, Proof of Concept)
  - Phase III (Efficacy)
  - Phase IV (Post-marketing)
- All correspondence with regulators, including meeting minutes
- Costs related to drug discovery and development, manufacturing, marketing and distribution
Most information and data described above are normally part of the Investigational New Drug (IND) application and are not obtainable under the Freedom of Information Act (FOI), even after the drug is approved. Some FDA materials and correspondence related to each drug candidate is discoverable after a drug has been approved, limited to parts of the actual New Drug Application (NDA) itself. Also, high-level results of some pre-clinical and clinical studies are often presented at conferences or published in journals, but typically only if positive results are achieved. Such abstracts, presentations, and articles may contain rudimentary information on study designs and analyses, but are inadequate to allow independent verification of results.

The proposed OSRD paradigm proposes to make transparent much of what is kept proprietary as outlined in Table 5 above, with the following exceptions:

- Molecular/Chemical Structure
- Synthesis and Manufacturing Processes
- Some Clinical Trial Data and Analysis (until after un-blinding of treatment assignment in controlled, blinded studies).

The purpose of keeping the first two items proprietary is so developers can protect the patents on their intellectual property and ultimately have a drug to sell if it is approved by regulators. Otherwise, other drug manufacturers could steal, manufacture and market the drugs, perhaps in other countries with lower regulatory standards or enforcement. The purpose of keeping the third item proprietary until after un-blinding is to avoid introducing bias into comparative clinical trials.
In the proposed OSRD process, all other information that makes up most of the IND and NDA, including study protocols, study data, analysis programs, IND safety updates, and written interactions with regulators, could be made available in an ongoing fashion during the R&D process. Full and timely disclosure of most of the contents of the IND could be made a pre-requisite for filing the NDA, thereby truly opening up the R&D process.

In summary, this research examines whether an OSRD approach to pharmaceutical R&D could lead to better designed and more efficient drug development plans and processes, resulting in better study designs, higher quality data and analysis, and lower R&D costs.

**Research Questions**

Primary Research Question:

- Overall, would an OSRD paradigm for pharma R&D be feasible and desirable in terms of process quality and efficiency, as defined by the key informants?

Secondary Research Questions:

- What are impressions of the current process of R&D in terms of process quality and efficiency?
- Would OSRD have a positive, negative, or neutral impact on the quality of clinical research design, conduct, analysis, and results overall?
Would OSRD have a positive, negative, or neutral impact on the efficiency (time and/or costs) of clinical research design, conduct, analysis, and results overall?

Regardless of whether or not the key informants support OSRD, do they recommend other and potentially better innovations applicable to pharma R&D?

What would the scientific, regulatory, legal, policy, financial and operational barriers be to implementing an OSRD approach?
Chapter 4: Methods

Data Source: Key Informant Interviews

To answer the primary and secondary research questions, qualitative data were collected from key informants using a semi-structured questionnaire and interview format (Appendix 5). The choice of key informants and interview questions were intended to encompass the full range of information relevant to pharma R&D including patient privacy, intellectual property and patent law, regulatory oversight, science, healthcare financing, information technology, policy, politics and marketing.

The key informant interview methodology is well suited for exploratory research such as a new and hypothetical OSRD paradigm. Moreover, the primary endpoints, pharma R&D quality and efficiency, at this time are ill-defined under the current R&D model, therefore providing no credible baseline on which to build a more quantitative research methodology.

Finally, it would be impractical to rapidly pilot-test OSRD by applying it to some pharmaceuticals in development, and then comparing the efficiency and quality of OSRD versus pharmaceuticals developed under the traditional paradigm.

In other words, there are currently no quantitative means by which to determine, for example, ‘an OSRD process would be XX% more or less expensive per approved drug,’ or ‘require YY more or less years to move from discovery to
approval.’ The qualitative key informant approach is therefore ideally suited to investigate a hypothetical pharma R&D process such as OSRD to assess its potential feasibility and acceptability.

**Identifying Key Informants**

Key informants were contacted representing three major stakeholder groups: academia, industry, and regulatory authorities, as shown in Figure 4. Academics were sought in order to gather feedback from researchers that were more likely to be open to innovations that challenge the current drug R&D process. Industry representatives were interviewed as it was initially assumed that they would be the most invested in the *status quo*, the current drug development process, and therefore the most resistant to change. Moreover, pragmatically, it is unlikely that the pharma R&D process can be modified without buy-in from industry, and therefore it was important to gauge pharma’s appetite for change. Finally, regulators were interviewed because changes to the R&D process could have an impact on the future approvability of drug candidates, and therefore regulatory support for any major innovation is critical.

Senior scientists, executives, and regulators were chosen from organizations such as the following:
Academia

- Cleveland Clinic Coordinating Center for Clinical Research, Duke Clinical Research Institute, Harvard Clinical Research Institute, etc.

- Various healthcare economics, financing, patient advocacy groups, and/or policy organizations (e.g. Open-Science In Drug Discovery, Clinical Trials Transformation Initiative)

Industry

- Pharmaceutical, device and/or diagnostic development companies, both “Large Pharma” and smaller “Biotechs”

- Contract Research Organizations, to which pharmaceutical companies typically outsource R&D (e.g. Quintiles, PPD, PRA)

Regulatory

- US FDA, EMA

Note that the above list of organizations is illustrative in order to protect the confidentiality of the key informants who actually participated in the interviews. The initial target number was 3-4 senior representatives from each stakeholder group or until saturation was reached. Saturation in this context refers to the situation where little or no new insights or information is gained from each additional key informant.53
Recruiting Key Informants

The process for recruiting potential key informants included the following steps:

1. Potential participants were contacted via e-mail or letter (Appendix 1) to ascertain interest in participating in research regarding general innovations to the current paradigm for pharma R&D.

2. Potential participants were provided with a brief description of the proposed hypothetical OSRD model (Appendix 2).

3. Potential participants were given an Informed Consent Form (Appendix 3) prior to seeking verbal consent and encouraged to contact the researcher with any questions or concerns regarding participation. Verbal consent was obtained immediately prior to conducting an interview.

4. Thirty-to-60 minute interviews were scheduled and conducted in-person or over the telephone.

IRB Review

As the key informants were not a vulnerable population, the information sought in the interviews was not particularly sensitive, and the likelihood of breach of confidentiality was low, the UNC Biomedical Institutional Review Board (IRB) granted an exemption on 4 June 2012 for the key informant interviews and approved a request for a verbal consent process (Appendix 6).
Confidentiality Issues

In order to protect the confidentiality of the key informants, information about their roles and experience was reported in the aggregate. Many participants had multiple degrees, but only one degree was reported. Masculine pronouns (he, his) were used regardless of the sex of the participant. Finally, when referring to someone’s role such as CEO, Senior Regulator, or Academician, the active tense is used, suggesting that they were in the stated role during the time of the interview even though they may not have been (e.g. retired). The title or role reported represents the highest or the longest role in duration in their careers at the time of the interview.

Also, throughout the paper attributed quotes are used, for example in the Review of the Literature and also the Discussion chapters. Note that none of the attributed quotes came from people who were also key informants for the research.

Data Collection Procedures

Interviews were recorded when permitted by the respondents and notes taken by the interviewer in all cases. In some cases, the key informants referenced or provided additional materials to support their comments. Immediately after the interview, the interviewer clarified and/or amended the interview notes (Appendix 4).

All recorded interviews were transcribed. To protect key informant confidentiality, all transcripts (Microsoft Word documents) were password protected, the key informant’s identifying information (title, employer, etc.) were deleted, and
their names were replaced with a letter/number code. The key for identifying which code corresponded to which interview was maintained in a password-protected Microsoft Excel file.

**Data Management and Analysis Plan**

The transcribed interviews were coded and analyzed manually, using the Coding Manual developed for this research and presented in Appendix 7. The quotations reported here are predominately verbatim, with minimal editing in order to remove information that might compromise the confidentiality of the participant. When such edits occur to directly quoted responses, the edits are identified by brackets such as *edited text inserted by researcher* and/or ellipses [...] to represent deleted material. Furthermore, the quotations imbedded in the text of the dissertation at times were edited to improve flow and clarity while seeking to avoid any corruption of the key informant’s intent. However, the transcribed quotations in Appendices 8 - 10 are excerpted from the interviews but generally not edited for flow or clarity.
Chapter 5. Results

Characteristics of Interviews and Key Informants

Sixteen potential key informants were contacted; one regulatory representative did not respond to the recruitment e-mail and one academic representative agreed to be interviewed by telephone but did not attend as scheduled. Attempts to reschedule were unsuccessful. Therefore, fourteen interviews were conducted between 18 June and 10 December 2012. Ten of 14 interviews were conducted by telephone, and all but one key informant agreed to have their interview audio recorded. One participant asked for and received the interview questions in advance and provided a written response prior to the interview, which then proceeded as planned. A summary of the interviews and the key informants’ backgrounds is provided in Table 6.
Three key informants each were interviewed representing the academic and regulatory stakeholder groups, whereas the remaining eight have spent the majority of their careers in industry, either at CROs and/or in pharma companies. Aggregate data on the key informants and interviews are reported in Table 7:
Table 7. Aggregated data on key informants and interviews

<table>
<thead>
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<th>Variable</th>
<th>Category</th>
<th>n</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stakeholder Group</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Academia</td>
<td>3</td>
<td></td>
<td>21.4%</td>
</tr>
<tr>
<td>Industry</td>
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<td></td>
<td>57.2%</td>
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<tr>
<td>Regulatory</td>
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<td>21.4%</td>
</tr>
<tr>
<td>Total</td>
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<td></td>
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<tr>
<td><strong>Sex</strong></td>
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<tr>
<td>Male</td>
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<td></td>
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<tr>
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<td>35.7%</td>
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<tr>
<td>Total</td>
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</tr>
<tr>
<td><strong>Race</strong></td>
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<td></td>
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<td>Caucasian</td>
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<td></td>
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<tr>
<td>Total</td>
<td>14</td>
<td></td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Degree</strong></td>
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<td></td>
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<tr>
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<tr>
<td>PhD</td>
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<td></td>
<td>28.6%</td>
</tr>
<tr>
<td>Other</td>
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<tr>
<td>Total</td>
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<td></td>
<td>100.0%</td>
</tr>
<tr>
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<tr>
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<tr>
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<td></td>
<td>7.1%</td>
</tr>
<tr>
<td>Total</td>
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</tr>
<tr>
<td><strong>Interview Format</strong></td>
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<td>Telephone</td>
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<td>71.4%</td>
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<tr>
<td>F2F</td>
<td>4</td>
<td></td>
<td>28.6%</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td></td>
<td>100.0%</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>60.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>49-72</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drug R&amp;D Experience (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>25.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>12-40</td>
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<tr>
<td><strong>Interview Length (minutes)</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>44.7</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>25-90</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Two-thirds of key informants were male and all were Caucasian. Over three-quarters had an MD and/or PhD. The three regulatory representatives were very senior officials, and the three academicians were tenured, full professors or equivalent. Among the eight industry participants, five were Chief Executive Officers (CEOs) and/or Presidents of their respective companies, one was a Chief Medical Officer (CMO) in small Pharma and a CRO, and two were Vice Presidents (VPs) in large pharma. All but one participant had at least 20 years of experience in drug development.

As will be shown in the results that follow, there was a high-level of consistency and overlap among the interviewers, thus suggesting that data saturation was reached. Moreover, when designing the study methods, it was presumed that academics and regulators would tend to be supportive of greater transparency and collaboration, whereas industry representatives would tend to be more critical of OSRD. Therefore, it was possible that data saturation could be reached with a small number of academic and regulatory participants. However, support for OSRD and similar innovations was higher than anticipated among the industry representatives interviewed. Therefore, although data saturation was reached earlier in the data collection process, additional industry representatives were interviewed in order to uncover if possible critical and opposing views to OSRD.
Key Topics and Findings

Several topical areas emerged from the interviews based on the questions asked (Appendix 5). Seven major topics discussed included the key informant’s responses to:

I. Current state of pharma R&D;
II. Potential impact of OSRD on pharma R&D quality;
III. Potential impact of OSRD on pharma R&D efficiency (time and costs);
IV. Other potential impacts of OSRD;
V. Other innovations than OSRD that should be considered;
VI. Barriers to implementing OSRD to more mainstream pharma R&D; and
VII. Opportunities for implementing OSRD to more mainstream pharma R&D.

Each topic is discussed below, with quotes from the key informants whenever relevant, and with additional quotations provided as noted in Appendices 8, 9 and 10.

I. Impressions on the Current State of Pharma R&D

Each interview began with a question about the participant’s views on the current state of pharma R&D in terms of quality and efficiency, to serve as a baseline with which to compare potential innovations including OSRD. The responses were generally favorable in terms of the quality of R&D as it is conducted today. For example, one large Pharma VP stated:
“pharmaceutical R&D process as it is practiced by major ethical pharmaceutical companies is one of very high integrity.” VP, Large Pharma

The context here was that the quality of R&D is very high, particularly in regards to patient safety and data quality. The head of a CRO stated that he believes:

“there is sincere intent for high quality throughout all sectors of pharma R&D.”
CEO, CRO

Likewise, a CMO from a large CRO commented favorably on quality in the current approach to R&D:

“From the standpoint of a) scientific rigor, and b) the necessary controls around ensuring that from the very beginning of discovery all the way through to regulatory approval and use of a product in humans, I would grade the quality of it around 80 – 90%. It meets the mark in terms of internal control over what works, what doesn’t work, why it doesn’t work, and drugs washing out of the development program because they don’t meet milestones.”
CMO, CRO

However, in contrast, a large pharma representative was more cautious, stating that he had:

“more ethical concerns” and that “the danger now is that decisions are made at a higher level, possibly with more business interest than quality and patient safety.” VP, Large Pharma

This large pharma VP expressed concerned that when business interests override ethical concerns, this can lead to problems such as with Avandia™ (rosiglitazone), a diabetes drug where a pharmaceutical company pled guilty to intentionally withholding negative safety data to improve likelihood of approval.54
However, when asked about the efficiency of the current pharma R&D model, in terms of costs and time, the key informants were almost universally negative. The negative feedback included:

“The clinical side of it keeps getting longer. Well, not so much longer, but costlier and with poorer success rates. That is a big concern.” **Academician**

“*R&D is very slow*” and the “costs are ungodly”. **VP, Large Pharma**

“It’s terrible because it is so costly and [pharma has] such poor success rates – the predictability of their models are so bad”. **Senior Regulator, FDA**

Countering this nearly unanimous criticism only one participant, a VP from large pharma, had more positive feedback on the efficiency of R&D as it is currently practiced, stating:

“The issue of whether the system itself is efficient or not… the processes themselves have, in the short run, a tendency to be somewhat less efficient, but in the long run, in the end, when you stretch it out and calculate it, it is probably sufficient in order to support the value proposition and the investment.” **VP, Large Pharma**

When prompted with published concerns that the current drug development process is too inefficient to be sustainable,¹ this same VP replied:

“This is the most profitable industry in the history of free enterprise. The profitability in the pharmaceutical business is extremely high... So, I do not [agree with] people saying that the cost of the pharmaceutical R&D is not sustainable.” **VP, Large Pharma**

In summary, the general consensus was that the current process for pharma R&D is good in terms of quality, particularly when quality is defined as pharma
researchers exhibiting ethical behavior and a high regard for patient safety. However, even with the very positive views expressed by one VP from large pharma, the overwhelming view was that the current process for pharma R&D is very inefficient and unsustainable in terms of costs and time.

Additional comments on the efficiency of the current pharma R&D process are in Appendix 8.

II. Advantages and Disadvantages of OSRD for R&D Quality

Key informants were then reminded of the proposed OSRD paradigm and asked to consider whether OSRD could have a positive, negative, or neutral impact on R&D in terms of quality and efficiency. Beginning with quality, nine of the 14 participants (64.3%) indicated that they thought that an OSRD approach would have a positive effect, with over 35% indicating a neutral or negative effect (Table 8).
Table 8. Potential effect of OSRD in terms of R&D quality (positive, negative, or neutral); Aggregated for all participants

<table>
<thead>
<tr>
<th>Effect</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>9</td>
<td>64.3</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>7.1</td>
</tr>
<tr>
<td>Neutral</td>
<td>4</td>
<td>28.6</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>100</td>
</tr>
</tbody>
</table>

Next, to explore whether there were different perspectives between stakeholder groups, responses were broken out as reported in Table 9.

Table 9. Potential effect of OSRD in terms of R&D quality (positive, negative, or neutral); by stakeholder group

<table>
<thead>
<tr>
<th></th>
<th>Positive n (%)</th>
<th>Negative n (%)</th>
<th>Neutral n (%)</th>
<th>Total n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Academia</td>
<td>2 (66.7)</td>
<td>0 (0.0)</td>
<td>1 (33.3)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Industry</td>
<td>4 (50.0)</td>
<td>1 (12.5)</td>
<td>3 (37.5)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Regulatory</td>
<td>3 (100)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>9 (64.3)</td>
<td>1 (7.1)</td>
<td>4 (28.6)</td>
<td>14 (100)</td>
</tr>
</tbody>
</table>
These data suggest that regulators and to a lesser degree academicians perceive that OSRD would have a generally positive impact on the quality of R&D, whereas industry representatives opinions were split. While four industry participants felt positive about OSRD and the potential impact on study quality, an equal number were neutral (three) or negative (one). For the neutral participants, a concept expressed by all three was that quality of R&D was already very high, therefore the potential for any innovation, OSRD or otherwise, to improve quality is limited.

Industry perspectives on any positive, negative or neutral impacts of OSRD on quality were varied, as is evidenced by these three quotes:

*If when you say* quality, you mean more information that would lead to better decision making or better outcomes, the answer would be yes. I don’t know if it would improve the quality of the study from the perspective of data quality, but certainly more information is always better than less. CEO, CRO

Would [OSRD] produce a higher quality? The answer is no because I believe that the quality has to be built into the system from the integrity point of view. Would it impact integrity? I do not think so… [Therefore] I do not think it would have an effect on quality at least as I define it. VP, Large Pharma

*I think that the impact on quality would be neutral, in terms of research design, conduct, analysis, and results… those terms seem more related to efficiency than quality.* President, CRO

Therefore, there was no clear consensus that more transparency and collaboration would have an impact on R&D quality.

Additional quotes from all three stakeholder groups regarding OSRD and quality are in Appendix 9.
III. Advantages and Disadvantages of OSRD for R&D Efficiency

Overall, the key informant comments reflected a strong but not unanimous belief that OSRD would have a positive impact on efficiency (Table 10).

Table 10. Potential effect of OSRD in terms of R&D efficiency (positive, negative, or neutral); Aggregated for all participants

<table>
<thead>
<tr>
<th>Effect</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>12</td>
<td>85.7</td>
</tr>
<tr>
<td>Negative</td>
<td>1</td>
<td>7.1</td>
</tr>
<tr>
<td>Neutral</td>
<td>1</td>
<td>7.1</td>
</tr>
<tr>
<td>Total</td>
<td>14</td>
<td>100</td>
</tr>
</tbody>
</table>

Much more than the question regarding OSRD and quality, over 85% of participants expressed that OSRD would have a positive impact on R&D efficiency, meaning that it could reduce the current average time to gain approval to less than 12-15 years and reduce the current average costs from approximately $1 billion. Importantly, no key informant estimated the potential reductions, only that OSRD would likely have a positive impact of indeterminate magnitude.

Next, to explore whether there were different perspectives between stakeholder groups, responses were broken out and reported in Table 11.
Table 11. Potential effect of OSRD in terms of R&D efficiency (positive, negative, or neutral); by stakeholder group

<table>
<thead>
<tr>
<th></th>
<th>Positive</th>
<th>Negative</th>
<th>Neutral</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Academia</td>
<td>2 (66.7)</td>
<td>0 (0.0)</td>
<td>1 (33.3)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Industry</td>
<td>7 (87.5)</td>
<td>1 (12.5)</td>
<td>0 (37.5)</td>
<td>8 (100)</td>
</tr>
<tr>
<td>Regulatory</td>
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<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>3 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>12 (85.7)</td>
<td>1 (7.1)</td>
<td>1 (7.1)</td>
<td>14 (100)</td>
</tr>
</tbody>
</table>

Here there was a higher degree of consensus among the stakeholder groups, with only one academic and one industry representative expressing views other than positive. The negative view was that OSRD could lead to information overload as well as data misinterpretation by unqualified reviewers:

“[With OSRD], you would have a ton of data that you have to interpret somehow if you took it to its extreme where every single thing that the pharmaceutical company did would be public. That would be a disaster, because people cannot interpret data, animal safety data for example. There are multiple cases where you get some horrible toxicity in an animal and you find out that that particular species produces a metabolite that no other species including man produces and you are only going to see that toxicity in that species, but you find that out later on.

Therefore, it depends on who has access to the data and who is doing the interpreting and there is so much “crack-pot” science out there. All you need to do is look at everything from rejuvenation to penis enlargement. There is a lot of misinformation and a lot of misinterpretation of data. There would be too much data and it would be overload.” CEO, Small Pharma
This pharma executive went on to say:

“There is a premise there, I am not saying I disagree with, but also I am not saying it is true, and that is the odds of success in pooling the data go up enough to cover the decrease in return. I do not think that would happen. If you put five companies together, instead of getting one wise entity you simply have five entities coming together and still muddling through.” CEO, Small Pharma

This concern was mirrored by another in industry, where overall he thought that OSRD would improve efficiency but expressed this caution:

Now on the efficiency side, it is hard to argue that it would not be more efficient. The more information one has to consider in making your own decisions about the most efficient/cost effective and resource effective pathway to get to the end zone, the better… I think it is almost unarguable that it would be more efficient.

But, it could have one of two effects. Either it could be refreshingly revelatory and could encourage people to be hyper vigilant about the quality of the work that they do or it could have exactly the opposite effect and all work would essentially grind to a halt because [pharma would] be afraid of exposing a vulnerability.” CMO, CRO

These two key informants above voiced profound skepticism about OSRD, to the point that OSRD could be less efficient than the current paradigm. However, the vast majority of opinions across all three stakeholder groups were strongly positive, including:

“So I think in process innovation, [OSRD] can be very valuable… clearly can be very profitable at a very early stage, very useful, fruitful at a very early stage. I think it could be significant… I think there is a lot that could be done to speed up the process and also to make it more targeted… if you could decrease cost by 20%, that is a couple hundred million dollars.” Academician

“[OSRD] is definitely beneficial. There are currently a number of areas where investments by companies are duplicative, even if they are each aiming for somewhat different molecules.” Senior Regulator
“It is illogical to me to say we believe that the [OSRD] model is right for orphan or niche diseases [but not] also be right for bigger diseases. We are seeing with these orphan diseases data that improves the outcome in terms of approval times, time to market, and patient benefit. [Therefore], I find it illogical to say that the benefits [of OSRD] should not be extended to broader populations.” CEO, Large Pharma

This last quote from the CEO expresses a critical view as it directly addresses the question of whether OSRD could be beneficial for orphan indications but not for all indications. The CEO of a top-ten pharma company considers but then rejects this possibility.

Therefore, although concerns were raised, the vast majority of academic, industry, and regulatory representatives viewed OSRD as potentially beneficial in terms of improving the process of pharma R&D, thereby leading to quicker approvals and lower costs. Further comments on potential advantages and disadvantages of the proposed OSRD paradigm on efficiency are in Appendix 10.

IV. Other Potential Impacts of OSRD

In addition to providing feedback on the potential impact of an OSRD approach on R&D quality and efficiency, several key informants commented on OSRD and public relations and also on whether OSRD undervalues scientific know-how.
Public Relations

As noted in the Introduction, trust in the pharma industry is low and two key informants spoke about the value of more transparency helping the pharma industry overcome its negative image as untrustworthy. In recalling that pharma spends more for marketing than R&D, perhaps in small part to help burnish its poor reputation among physicians and patients, the participants responded:

“[OSRD] can help pharma from a public relations perspective, just like pharma tries to do with humanitarian efforts, to show that pharma cares about patients, not just profits.” CEO, CRO

“I think the impact of OSRD could be significant. Not only increasing the trust in the [R&D] process, but also showing a real desire for sharing of knowledge would be positive.” VP, Large Pharma

The VP of the large pharma company quoted above further commented that the public relations impact might be the most beneficial aspect of an OSRD approach, regardless of whether OSRD would reduce costs and development time.

Placing Value in the Molecule versus R&D “Know-how”

One key informant from industry correctly noted that the proposed OSRD paradigm places all of the value of a drug in development on the molecule itself. In other words, if the molecule is highly effective and has few side effects, then its value should be very high and, likewise, if the drug is ineffective and has many dangerous side effects, the value should be low. However, OSRD places little value in the “know-how” of pharma R&D, such as using scientific creativity to determine the optimal disease endpoints to study and the best study-designs for demonstrating
a positive drug effect. The proposed OSRD paradigm would continue to protect the structure of the molecule and means of synthesis (the intrinsic value of the molecule), but would not protect information on the process of designing, implementing, and analyzing study results (the intrinsic value of scientific know-how). OSRD also places no value on marketing. The CEO comments:

“The problem [with the proposed OSRD model] is that you are focusing on intellectual property (IP) when know-how and working knowledge are sometimes more important. So, if all your know-how and working knowledge are public, then it becomes potentially less attractive for an investor to invest in [a compound].” CEO, Small Pharma

However, this view was countered by other key informants, one each from industry and regulatory. The regulator raised concerns that valuing know-how actually undermines pharma R&D as a pursuit grounded in science, saying:

“The hallmark of science is the data are put in a public domain, they have to be replicable and they have to be subjected to rigorous, relentless scientific criticism and scrutiny and that is where the drug industry has erred over the past thirty or forty years because their practices and principles have been in secret. None of R&D has been out in the daylight and therefore we have not advanced science. We have advanced practitioners of the art [of pharma R&D], and maybe some practitioners are masters. They are craft masters, but not [scientists].” Senior Regulator

A CEO from large pharma rebutted the argument that OSRD undervalues know-how by simply stating that the value of a potential drug:

“…will be determined by the real profile of that drug once it gets into real clinics. That is where [pharma] should compete… profitability to me in this business should be, and I think increasingly is, directly proportional to the real innovation and the added benefit we bring to a patient.” CEO, Large Pharma

Then later in the same interview, this CEO from large pharma further expressed:
“I fully encourage my industry colleagues [to accept that] IP is IP. If you have good intellectual property, you will be recognized for that intellectual property.”

In other words, this CEO from large pharma agrees that OSRD does not place much value in know-how, but then states clearly that the value of a therapy should be in the molecule itself and whether it benefits patients, not in scientific know-how and marketing.

V. Potential Innovations other than OSRD

Each key informant was asked to comment on potential innovations other than OSRD that should be considered, whether or not the participant supported the concept of OSRD. The question read:

“Discussions about OSRD are essentially about innovating and improving clinical research. Are there other and potentially better innovations that should be considered?” Interview Question

As the key informants were very senior representatives of pharma R&D, the intent of the question was not only gather new ideas, but to also gauge OSRD’s relevance in the broader context of pharma R&D innovations.

However, no key informants responded with substantively different proposals. One participant noted:

“There are lots of opportunities for creativity and innovation [in basic science and drug discovery], but when we get into the development sciences, particularly the clinical and regulatory sciences, there are not too many ways left to skin the cat.” VP, Large Pharma
In fact, the two most innovative proposals from industry representatives involved expanding the proposed OSRD model, as opposed to avoiding an OSRD approach. In one instance, a VP from large pharma recommended that OSRD stakeholders be broadened to include the payers, meaning that both public payers (Medicare, Medicaid) and private insurance companies should be part of a more transparent approach.

*In the world we live in now, clinical and regulatory science is no longer the front runner for success. It used to be, but now it is not. Now it is payer reimbursement and market access… [Therefore, with OSRD], the collaborators could come together and define the criteria [to test safety and efficacy] and propose these to both the payers and the regulatory agencies.*

VP, Large Pharma

It should be noted that this same VP in large pharma at first maintained that the current pharma R&D model did not require significant innovation, as it is “the most profitable industry in the history of free enterprise” but later in the interview recommended that OSRD be expanded to include payers as a key stakeholder.

The other enhancement proposed for OSRD envisions a process where drug developers would develop potential therapies only through proof of concept (POC), or Phase I/II clinical trials. All the information collected to support a successful POC would be made public, so that the potential safety and efficacy could be assessed in an open and transparent environment. Then, the most promising compounds would undergo Phase III testing by researchers that the key informant referred to as “clinical research utilities”, perhaps with some similarities to other public utilities such as electric power or water treatment companies. He described these “utilities” as
research consortia that could be funded by pharma or government but do not profit by the sales of any approved drugs. In this R&D model, all profits would be realized at the end of POC. As with the POC data, the results of Phase III testing and interactions with regulators also would be made public.

The costs that accrue after POC (Phase III clinical trials, manufacturing, patient and provider education, and distribution) would determine the costs to consumers and would not include additional profits. Note that the key informant that suggested this approach, a CEO of small pharma, initially was by far the most skeptical that OSRD could have any benefit or is practicable. Nevertheless, when asked to suggest alternatives to OSRD, he responded with the modified OSRD approach that relied on “clinical research utilities” and then stated:

“I think that, if I were a dictator of the world, I would probably give a try or at least analyze the [modified OSRD] model that we just talked about.” CEO, Small Pharma

The overall result of the question regarding other potential innovations was that additional innovations were not championed. This conclusion reinforces the concept that OSRD has the potential be substantially innovative and positively impactful in improving the efficiency of pharma R&D, and perhaps the only viable new option available to “skin the cat”, as phrased by one key informant.

VI. Barriers to Implementing OSRD

To many of the key informants, broader transparency and collaboration may be a too radical divergence from the standard practices in the pharma industry.
Therefore, even exploring the OSRD concept would be unacceptable, regardless of whether it might be beneficial in terms of quality, time, or costs. In the words of a VP from large pharma, even the potential of a negative impact on competition and maximizing profits would render OSRD a non-starter:

“Anything that is going to [be perceived to] diminish the incentive of the industry to develop drugs is counter-productive… if you lose your proprietary interest or competitive advantage it would make the drug far less competitive and therefore that is your biggest impediment to [OSRD] ever being adopted.”

VP, Large Pharma

Likewise, an academic who expressed that he was very much in favor of OSRD regulations from an ethical and public health point of view, was also skeptical about OSRD:

“I am in favor of greater transparency, but I am in favor of greater transparency by forcing greater transparency. I have been an advocate for laws and rules about hiding data that are of value to the public health… However, [any greater transparency has] been achieved with the industry kicking and screaming the entire way. Not because [the pharma industry] thinks it is in their interest.”

Academician

This academician felt strongly that the possibility that industry could ever voluntarily embrace OSRD was so unrealistic as to not merit serious consideration, declaring:

“Oh come on, [voluntarily implementing OSRD] is the silliest thing I have ever heard. They have all the moral fiber of convicted criminal… it is not going to happen. It is not the way the industry works.”

Academician

The view that the pharma industry would only collaborate and share information if required by laws or regulations was echoed by a regulatory representative:
“I do think it would be hugely helpful although I think that there are legal barriers to doing this. [Industry] would have a fleet of lawyers throwing themselves on the Capitol steps [of Congress] demonstrating.” Regulator

Therefore, representatives from all three stakeholder groups believed the chief barrier to OSRD would be industry concerns regarding a potential negative impact on profits and that such resistance to any change is entrenched. Moreover, assuming that any innovation cannot be empirically proven to improve efficiency a priori, then these key informants opined that industry would resist any unproven innovation, including OSRD:

“No one has ever really tested it. And who is going to stick their neck out to test it? [OSRD] is a theory. There is no tangible, measureable effect and so you would ask the pharma industry, on the basis of blind faith, to be willing to put our information in the public domain because we think it might have benefit.” Academician

This barrier should be coupled with the concerns raised in the OSRD and Efficiency results above, namely information overload and fear of exposing vulnerabilities about a pharma developer’s compound (Section III).

Therefore, in summary, four barriers were proposed by the key informants, including concerns about: 1) information overload, 2) negative impact on competitiveness in general and on maximizing profits in particular, 3) keeping information proprietary is too entrenched in the pharma industry to ever change, and 4) any benefits of OSRD being unproven. As stated by participants from academia and industry, simply the potential for negative impacts is enough to keep industry from meaningfully considering OSRD.
VII. Opportunities for Implementing OSRD

However, throughout the interviews the key informants also provided examples of how proponents for more transparency and collaboration could address and, in some cases, already are addressing the barriers noted above.

Overcoming Barriers: Information Overload

One key informant asked during the interview what barriers were being proposed by the other participants, and when told of the concerns about too much data leading to “analysis paralysis”, he dismissed the concerns by responding:

“In response to the concern of information overload, you always have a choice about what pieces of information you want to spend a lot of time analyzing and pursuing. I would rather be given the choice of looking at as much information I chose to look at rather than being in a position where I was not allowed to look at some information that might be helpful.”  
CEO, Large Pharma

Overcoming Barriers: Negative Impact on Profits

In Section III above, “OSRD and Efficiency”, the vast majority of key informants felt that more transparency and collaboration would have a positive impact on efficiency and costs, and therefore on overall profitability. Thus, historical assumptions regarding the value of keeping information proprietary may be giving way to theories that information sharing can improve efficiency and therefore be positive to profitability. This softening of concerns about OSRD and profit-erosion among the senior leaders of pharma R&D is reflected in following observation from an industry representative:

“I think there is openness to it now that five years ago frankly would not have been there.”  
CEO, Small Pharma
Overcoming Barriers: Keeping Most Information Proprietary is Entrenched

Several key informants expressed reservations that the pharma industry could ever be flexible to OSRD, as the practice of keeping most information proprietary is entrenched, even information not protected by patents. However, representatives from all three stakeholder groups pointed out that much of the information pharma attempts to protect is, in practice, not kept proprietary. The three following quotes support this view:

“There really is not that much in the way of true trade secrets.” **CEO, Large Pharma**

“[The FDA] would like to aggressively narrow what is considered commercially confidential or a trade secret. For example, [pharma companies give] the protocol out to all the investigators. It is just hard to imagine how it could be that confidential. All the IRBs see it. It is a fiction that the protocol is a heavily guarded secret.” **Regulator**

“Solving the challenges of designing the protocols and collecting and analyzing the data, I know people have treated it as proprietary in the past, but to some extent that is a farce. We need to be explicit about that. In addition, this idea of confidentiality is getting in the way all over the place. I know it is not enforceable, people have these confidentiality agreements that just are not enforced.” **Academician**

This academic was then asked, if keeping information proprietary is not enforceable, would more transparency and collaboration be positive, neutral, or have unintended negative consequences. To this he replied:

“I think if you make an argument that you are already sharing data and pretending you are not, then currently you just have all the downside of information and data sharing. So, perhaps if we went to the other extreme [and adopted OSRD], to some extent you should only have upside. Whatever
negative impact information sharing can have should be out there already.”

Academician

This academic representative made the argument that to a large degree transparency is already in place, that more transparency and collaboration is inevitable, but that “confidentiality is getting in the way all over the place”. The implication is that unintended transparency, as opposed to planned and organized information sharing, is less efficient. Supposing that widespread information sharing is inevitable, then the question no longer should be, ‘Is OSRD good or bad for the pharma industry?’ Perhaps the question should be, ‘What is the most efficient and practical way to share information?’

Key informants from all three stakeholder groups responded that the concept that information is in actuality being kept proprietary is “a farce”, supporting the concept that OSRD to some extent already exists, but simply not in an organized and most efficient way. Moreover, if more transparency is inevitable, then any psychological entrenchment against OSRD increasingly becomes less relevant.

**Overcoming Barriers: Benefits of OSRD Unproven**

Two key informants, one each from academia and industry, discussed the more traditional model of transparency and collaboration in pharma R&D, where typically two companies sign an agreement to jointly develop and/or market a treatment. This traditional joint development approach is not broad, where information is shared among all stakeholders, but nevertheless demonstrates the
pharma industry’s historic openness to collaboration and data sharing, at least under certain, restricted circumstances.

However, seven of the key informants, representing all three stakeholder groups, referenced examples of OSRD-like initiatives, namely voluntary efforts that require broad transparency and collaboration among pharma companies and other stakeholders for the benefit of general R&D efforts. Their examples included those referenced in the Literature Review (Chapter 2) such as the DNDi and TransCelerate, but also several more. Table 12 provides a brief description of the initiatives highlighted by the key informants.

Table 13 subsequently examines these eight initiatives to identify which of the OSRD components described in Table 5 are applicable. This assessment of the OSRD-like qualities of the initiatives are the interpretation of the author, deduced from what is often limited information about the structure and activities of these initiatives. Note also that when companies collaborate to share data, this in all likelihood does not mean that data are shared without restrictions. For example, with the Cystic Fibrosis Foundation (CFF) efforts, only placebo data from clinical trials are shared.

DNDi represents the initiative that most closely resembles the OSRD process proposed by this research, however it only applies to NTD. Transcelerate is noteworthy in that, while it does not share study designs and data, it is not restricted to NTD or Orphan diseases and is therefore intended to make all drug development more efficient.
Table 12: OSRD-like initiatives already occurring in pharma R&D

<table>
<thead>
<tr>
<th>Initiative</th>
<th>Description</th>
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<tbody>
<tr>
<td>CEO LSC(^{55})</td>
<td>CEO Life Sciences Consortium. Founded in 2005, a task force of the CEO Roundtable on Cancer. As part of Project Data Sphere, coordinates data sharing by developers of cancer biomarkers and therapies.(^{48})</td>
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<tr>
<td>CFF(^{56})</td>
<td>Cystic Fibrosis Foundation assists multiple pharma companies developing treatments for CF. Placebo data are pooled across datasets from multiple companies to provide baseline and natural history information on CF. If a company is willing to provide their placebo data, then they can see everyone’s placebo data.</td>
</tr>
<tr>
<td>DNDi(^{57})</td>
<td>Drugs for Neglected Diseases Initiative. Founded in 2003, Pharma and foundation funded. Described in the Literature Review.</td>
</tr>
<tr>
<td>HIV Drug Development</td>
<td>Not a separate entity or initiative per se. Several key informants referenced the voluntary collaboration exhibited by pharma companies in jointly developing combination therapies, or HIV treatment “cocktails”, which are in wide use for HIV anti-retroviral therapy.</td>
</tr>
<tr>
<td>iSAEC(^{58})</td>
<td>International Serious Adverse Event Consortium. Founded in 2007, comprised of members from pharma, foundations, and regulators. “The mission of the iSAEC is to identify DNA-variants useful in predicting the risk of drug-related serious adverse events.”</td>
</tr>
<tr>
<td>OMOP(^{59})</td>
<td>Observational Medical Outcomes Partnership. Founded in 2007, a public-private collaboration that includes PhRMA, FDA, and NIH to identify “the most reliable methods for analyzing huge volumes of data drawn from heterogeneous sources”.</td>
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<tr>
<td>SNP Consortium(^{60})</td>
<td>International HapMap Project. A public-private effort “to develop a public resource that will help researchers find genes associated with human disease and response to pharmaceuticals.”</td>
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<tr>
<td>TransCelerate(^{61})</td>
<td>Described in the Literature Review. Industry funded initiative founded in 2012 to collaboratively “develop shared industry research and development solutions to simplify and accelerate the delivery of innovative products to patients”.</td>
</tr>
</tbody>
</table>
Table 13: How ongoing OSRD-like initiatives compare with proposed OSRD model

<table>
<thead>
<tr>
<th>Initiative</th>
<th>Molecular structure</th>
<th>Synthesis &amp; Manufacturing</th>
<th>Discovery</th>
<th>Pre-clinical /Animal</th>
<th>Clinical</th>
<th>Regulatory Information</th>
<th>Cost data</th>
<th>Co-investment</th>
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<tr>
<td>CEO LSC$^a$</td>
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<td>CFF$^b$</td>
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<td>DNDi</td>
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<td>HIV Drug Development</td>
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<tr>
<td>iSAEC$^c$</td>
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<td>OMOP$^d$</td>
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<tr>
<td>SNP Consortium$^e$</td>
<td>n/a</td>
<td>n/a</td>
<td>x</td>
<td>n/a</td>
<td>n/a</td>
<td></td>
<td>n/a</td>
<td>x</td>
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<tr>
<td>TransCelerate$^f$</td>
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</table>

$^a$ Only data for developing bio-markers and therapies

$^b$ Only placebo data from clinical trials

$^c$ Only serious adverse event data

$^d$ Only sharing data on study designs and methods, not actual data and results

$^e$ Basic science

$^f$ Shares what is deemed “pre-competitive” information such as data on clinical trials investigative sites

$^g$ Co-investment describes where pharma companies, foundations, governments, etc. are jointly funding the initiatives
While these efforts are not officially labeled OSRD, they nevertheless are aligned with the foundation of any OSRD paradigm, mainly broad transparency and collaboration. Thus, for this research, these examples are classified as “OSRD-like” initiatives or efforts.

The OSRD-like initiatives in Tables 12 and 13 have been in place, in some cases, for more than ten years, have wide support in the industry, and depending on the initiative and length of time since each have been established, have a history of success. Therefore, several of the key informants commented that a foundation is already in place to allay concerns that OSRD is radical and unproven, as reflected in this quote:

“There are a lot of little pockets of good things that have happened that people [in the pharma industry] have either, a) been unaware of, or b) not been willing or open to think about. I think now is a time when there is much more openness to the concept.”  CEO, Small Pharma

Summary of Results

Several key informants in all three stakeholder groups acknowledged that transparency and collaboration are advantageous from a scientific, patients’ rights, and population health perspective. There was no dissenting view on these three points, even from those key informants most critical of OSRD. Furthermore, the majority of participants supported the concept that OSRD could improve efficiency by reducing the time and costs required to amass the data required to gain regulatory approval and payer reimbursement.

A key purpose of this research was to explore whether there also may be a business case for OSRD. Twelve of 14 key informants (86%) expressed a view that
OSRD would be more efficient, but would improving efficiency offset any loss of competitive advantages by sharing trade secrets? In the words of one key informant:

“So I think in process innovation, [OSRD] can be very valuable… clearly can be very profitable at a very early stage... I think it could be significant… I think there is a lot that could be done to speed up the process and also to make it more targeted… if you could decrease cost by 20%, that is a couple hundred million dollars [per each approved drug].” Academician

It is remarkable to note that most key informants, including the industry executives, expressed a belief that OSRD would improve efficiency and thereby decrease R&D costs. Therefore, even if sharing proprietary information and know-how could have a negative impact financially, any negative impact could be more than offset by a positive impact on efficiency. This support for OSRD in terms of potential financial benefit is a critical finding, as businesses understandably would resist vigorously any efforts that are perceived to have a negative impact on profits. The following quote sums up the findings that transparency and collaboration overall could be financially beneficial to business:

“Profitability to me should be and I think increasingly is, directly proportional to the real innovation and the added benefit we bring to a patient. And I would argue that the biggest challenge I see in our industry is getting to the market as quickly as is feasible based on the soundness of your data. If you share more information, your data ultimately will be stronger.” CEO, Large Pharma
Chapter 6. Plan for Change

Given the strong although not universal consensus among the key informants that OSRD could be beneficial overall, even to the business interests of the pharma industry, then what must happen to encourage the global drug development enterprise to explore and potentially adopt OSRD concepts? A major component of the interview process was to explore perceptions about likely obstacles and garner recommendations for the best pathway or pathways to implementing some form of OSRD. Therefore, interview data were used to develop a proposed plan for change.

Any significant change in the current process for R&D likely requires a paradigm shift, as described by Thomas Kuhn in The Structure of Scientific Revolutions. Kuhn is concerned with the nature of scientific inquiry and discovery, whereas this research is focused on the process of pharmaceutical science, not the scientific outcome per se. Nevertheless, significant innovations in the conduct of science, OSRD or otherwise, requires a “scientific revolution” in the words of Kuhn, and thus his insights are relevant. First and foremost, Kuhn states “any scientific group [cannot] practice its trade without some set of received beliefs” (pg. 4). In pharma R&D, the assumption that virtually all actions from drug discovery to commercialization must remain proprietary to protect and maximize business interests is such a “received belief” that has been, until recently, unchallenged. Kuhn also proposes that any data that challenge a paradigm will be resisted until they can
no longer be dismissed, and only then can a paradigm shift occur to accommodate the new data.

Pharma developers must start with 5,000-10,000 drug candidates to get one drug approved, and over 50% of the drugs that go into Phase III clinical testing fail, thus data suggest that current pharma R&D process is ineffective. Current R&D processes that are based on avoiding transparency and collaboration average 12-15 years to gain a drug approval with average costs of $1 billion, and this is credible data that pharma R&D as it is practiced is inefficient. These conclusions were widely supported by the key informants, where there was broad consensus that the current R&D processes are unsustainable. However, are these data compelling enough to shift the current R&D paradigm? In the words of one CEO from small pharma, “I think there is openness to it now that five years ago frankly would not have been there.”

If the key informants are correct in suggesting that the pharma industry may be open to a paradigm shift to OSRD, then what are the steps required to broaden the adoption of OSRD within the pharma R&D? John Kotter outlines an eight-part process to “successfully transform businesses”. Kotter proposes that for transformation to occur in a business or enterprise, all eight steps must happen and in the order presented (Table 14). While Kotter did not comment on the eight steps being used to transform an entire industry, the steps nevertheless serve as a useful framework for this Plan for Change.
Table 14: Kotter’s eight steps to promote transformational change

<table>
<thead>
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<th>Step 1</th>
<th>Establish a Sense of Urgency</th>
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<tr>
<td>Step 2</td>
<td>Form a Powerful Coalition</td>
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<tr>
<td>Step 3</td>
<td>Create a Vision</td>
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<td>Step 4</td>
<td>Communicate the Vision</td>
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<td>Step 5</td>
<td>Empower Others to Act on the Vision</td>
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<tr>
<td>Step 6</td>
<td>Plan For and Create Short-term Wins</td>
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<tr>
<td>Step 7</td>
<td>Consolidate Improvements and Produce Still More Change</td>
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<tr>
<td>Step 8</td>
<td>Institutionalize New Approaches</td>
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**Step 1: Establish a Sense of Urgency**

The primary driver for innovation in the conduct of pharma R&D is the time and relentlessly increasing costs of bringing drugs to market. At $1 billion for each approved drug, and perhaps as much as $10 billion or more at some of the largest pharma companies, the present R&D process is unsustainable in the opinion of many in drug development. When asked about what could drive substantial innovation in the R&D process, one key informant commented “the fear of death,” further noting that uncertainties and poor efficiency are driving investors and researchers away from pharma R&D. In terms of R&D efficiency, most agreed with the key informant who summed up the current situation as “terrible”.

Whether the current situation is in fact dire enough to create and sustain a sense of urgency is unclear, but the rapid increase in grey literature publications on
OSRD-like proposals in the last one to two years suggests that desire for meaningful innovation may be growing.

**Step 2: Form a Powerful Coalition**

Drug development has many stakeholders as described earlier – academia, industry, and regulators – but other key players as well, including patients and patient advocacy groups, payers, and politicians. Data therefore were gathered from three of these stakeholder groups under the assumption that innovation, OSRD or otherwise, is not possible without a broad support. That academic and regulatory participants generally embraced the proposed OSRD model is not surprising, and it is reasonable to assume that patients would also applaud greater transparency and collaboration such as that proposed in OSRD. However, this research also found a surprising level of support for OSRD among senior and chief executives in small and large pharma and CROs, which suggests that a broad and powerful coalition could be formed for innovations such as OSRD. While there are several OSRD initiatives for orphan diseases and NTD that are supported by industry, the high support among the industry participants interviewed for a broader application of OSRD is remarkable.

The group to organize and build a coalition should include all the major stakeholders, including the groups interviewed for this research, academia, industry, and regulators along with payers and patient advocacy groups. With the recent creation of TransCelerate to promote transparency and collaboration in R&D for pre-competitive information, perhaps it could be expanded to include all the stakeholders
and also broaden its mission to consider the OSRD paradigm proposed in this research.

**Step 3: Create a Vision**

A potential and broad vision for OSRD was proposed to the key informants, where the patentable information would remain proprietary (molecular structure and CMC), but virtually all other information would be shared with the goal of making the entire R&D process more efficient. While this vision was largely supported by the key informants, a detailed framework for exactly what is shared with whom and when, in what forum or format, is beyond the scope of this research and still needs to be explored. However, this is a critical step, as failing to adequately define the scope of OSRD, or any open innovation, can undermine any potential benefits.\(^{64}\)

**Step 4: Communicate the Vision**

As described in the Literature Review, there has been a sharp increase in grey literature on OSRD concepts in the last two years, and these discussions are beginning to be reported in the mainstream press, but less so in the peer-reviewed literature. In addition, there have been a handful of conferences or workshops on “open innovation” in R&D, such as the Amsterdam Conference on open innovation in R&D in April 2012, the Sage Bionetworks Congress in May 2012, and the Partnership in Drug Delivery conference in October 2012. The increase in grey literature and conferences on OSRD-like initiatives suggests an emerging discussion in the press and in public discourse, but at this early stage one open innovation proponent asked, “Are we spreading the word or preaching to the choir?”\(^{65}\)
Step 5: Empower Others to Act on the Vision

Again, at this early stage of OSRD, a codified vision has not emerged, and therefore no person or group is empowered to act. However, two foundational blocks are in place to foster this step.

First, this research suggests that pharma industry executives are open to the concept of OSRD and therefore these same executives, and their peers, may empower their staff to explore and implement OSRD concepts as they emerge. For example, pharmaceutical companies such as Eli Lilly, Novartis, and Pfizer recently have created “clinical innovation units”, not to innovate science, but to innovate the process of conducting clinical research. These and other large pharma companies are not only encouraging their staff to explore OSRD, but they are paying them to do so. Second, regulators and industry have already signaled their support of openness and collaboration in R&D with the announcements of DNDi and TransCelerate, as well as the other initiatives highlighted by the key informants in Table 12.

Step 6: Plan For and Create Short-term Wins

“So, I think the ideas [about OSRD] are good, but my feeling is that you have to have wins; you have to examples – case studies – to show these [OSRD concepts] are best practices.” CEO, Small Pharma

This is perhaps the greatest challenge to innovation in R&D, where the definition for "short-term" can mean years if not decades. Given that it takes 12-15 years on average to get a drug approved, even if OSRD could reduce the time to approval, it would be 10 or more years before we could verify the result. Moreover, several drugs must gain approval via an OSRD process to generate and verify data
on whether OSRD improves efficiency enough to offset any competitive advantages lost by sharing trade secrets. The need to approve several drugs via an OSRD approach could push the window for obtaining measurable OSRD results out beyond 20 years. For most people, 20 years does not constitute a short-term win.

It is also important to highlight here that OSRD is an example of process innovation and policy change, not scientific and technology innovation that can be comparatively rapid such as the development of the Salk polio vaccine and the antibiotic Penicillin. Research suggest that changes to processes, policies and regulations of the magnitude proposed here can take 20-40 years to develop, in particular because this will require “multiple-streams” of academia, government, industry, patients and patients’ rights groups, and regulators to reach and implement consensus.\(^6\) Healthcare reform in the United States and the recent Affordable Care Act (ACA) may be instructive here. The ACA is the latest major initiative in a healthcare reform process that has lurched forwards and sideways over the last century. In certain aspects pharmaceutical R&D innovation may be a smaller task than reforming all of US healthcare where pharmaceuticals are only a part of overall healthcare. In contrast, the task of implementing OSRD may in reality be more complex and time-consuming than the ACA as pharmaceutical R&D is a global enterprise, requiring input and buy-in from stakeholders around the world. Using an OSRD approach to make R&D more efficient would not work if only implemented in a single country. While scientific innovations sometimes accelerate understanding at blazing speeds, paradigm shifts and policy changes tend to lag. Therefore, at this stage the Plan for Change must rely on more long-term strategies and a flexible
approach in order account for the changes in data and opinion that inevitably will occur over the course of decades.

Nevertheless, several key informants stated that short-terms wins are needed and pointed to three types of examples, already completed or in process:

1. Basic Science and Drug Discovery: Many key informants gave examples of the benefits to pharma R&D of openness and collaboration in the areas of basic science, drug discovery, and biomarkers, citing examples such as the SNP Consortium and the CEO Life Sciences Consortium. The rationale here is that pharma researchers have already benefited from transparency and collaboration in basic science and discovery efforts, and these successes can be used to encourage clinical researchers to consider the concept of OSRD for Phase I-IV clinical trials.

2. NTD and Orphan Drug Initiatives: As with the DNDi described previously, if the industry sees that it is possible to develop drugs for tuberculosis or malaria more efficiently via OSRD, then momentum may grow within pharma to broaden OSRD concepts to mainstream drug development. In order for this to be most effective, then the DNDi must carefully track time and costs information so that the data can be compared with the efficiency of drug development under the current model.

3. Finally, while the first two short-term win options are largely driven from within the industry, three key informants stressed the importance of political or policy change, more driven from outside the industry. Examples here included the EMA’s commitment to proactively publish trial data
submitted for review and approval,\textsuperscript{21} the revision to the FDA Act in 2007,\textsuperscript{67} and the EXPERT Act approved by the US Congress in 2012.\textsuperscript{68} These are various legislative initiatives from the EMA and FDA intended to give the public more access to data and also to allow the FDA to collaborate with external experts on rare diseases, e.g. the EXPERT Act.

Therefore, there are some short-term successes already in place to help build momentum, but we must also be realistic that short-term for a paradigm shift of this magnitude could require 20 or more years.

**Step 7: Consolidate Improvements and Produce Still More Change**

Building from Step 6, there are several historic initiatives (SNP Consortium, iSAEC) that arguably helped foster more recent efforts (DNDi, TransCelerate). Within the Kotter framework, the concept of a continuous process of evaluation, or a feedback loop back to Step 3 (Create a Vision), is where the original vision should be modified as data are gathered and analyzed that offer insights on advantages and disadvantages of the proposed OSRD model.

Future research is needed in order to inform the process of producing “still more change”. In particular there are two efforts recommended:

1) Detailed time and cost data need to be collected by TransCelerate, DNDi, and any similar efforts to compare with historic time and cost data that were generated under the current pharma R&D processes.
2) Mathematical models need to be developed to test different assumptions, positive and negative, about the potential impact of OSRD on the time and costs of pharma R&D.

**Step 8: Institutionalize New Approaches**

As with Step 7, this step would take place in the future, if and when any improvements are in place. However, one recent example of transparency and collaboration, TransCelerate, is in itself a new non-profit company, funded by the pharma industry, which is designed to discover, implement, and institutionalize operational innovations. If successful, TransCelerate may serve as blueprint for ways to institutionalize innovations of any kind, OSRD or otherwise.

**Plan for Change: Next Steps**

The discussion of how Kotter’s Eight Steps can be applied to OSRD as described above is in most cases theoretical and beyond the scope this dissertation to implement. However, there are immediate steps that can be taken to maximize the potential value of this research.

1. In Kotter’s Step 6 (Short-term Wins), it is critical that TransCelerate and the DNDi compile and publish time and cost data that can be compared with earlier time and cost data in order to quantify any impact of OSRD on R&D efficiency. Therefore, an effort is underway with TransCelerate and the DNDi to schedule discussions by or before June 2013. The discussions are intended to understand if and how these groups are collecting time and cost data, and if and how they plan to analyze any
data against the current average estimates of $1 billion and 12-15 years for successful drug approvals.

If they have no plans to collect such data, then the goal of any meetings will be to generate support for such efforts within their organizations.

2. As this research suggests, the greatest hurdle to transparency and collaboration is the entrenched belief in the industry that while secrecy may be sub-optimal for science and patients, it is necessary to maximize profitability. Therefore, a critical next step is to explore creating economic models on any impact, advantageous or disadvantageous, that OSRD may have. Such models could be both micro- and macroeconomic.

On the microeconomic (compound) level, modeling could include exploring the potential impact of whether OSRD or any innovation could reduce timelines for submission, reduce costs, or both. Another component to be explored is whether OSRD would allow researchers to kill drug candidates earlier in the process. Recall estimates from key informants that over one-half of drug candidates fail in Phase III clinical trials. Therefore, even if OSRD would not reduce the cost of drugs that gain regulatory approval, a substantial net savings could be realized if the success rate were to increase, that is, candidates could be culled out based on poor safety and/or efficacy data earlier in the development cycle.

Regarding macroeconomic modeling, three issues need to be explored. First, it is possible that more transparency would foster more
collaboration when pharma companies are developing drugs for the same disease. Therefore, pharma companies could share the risk in terms of costs of drug development, but then also share the rewards, or profits, of any approved drug. Such a risk-reward model is already prevalent in the industry but is almost exclusive to two pharma companies conducting joint-development of a single compound. OSRD envisions the possibility that multiple pharma companies might collaborate on multiple compounds. Therefore, economic modeling should also explore what would happen if OSRD were to generate a better success rate, but that any profits would also be shared among multiple drug developers.

Second, economic modeling might include estimates on whether patent extensions or other incentives could be used to encourage drug developers to implement OSRD concepts before hard data on the impact of OSRD could be collected. In this second scenario, the industry might be induced to take a chance on OSRD but receive, for example, a two year patent extension. The approach of encouraging pharma to undertake innovative research initiatives by offering patent extensions and other financial inducements have been tried with some success with pediatric and Orphan drugs.

And third, modeling would need to include estimates of the costs of implementing OSRD. Investments, public and/or private would include
both the up-front costs of building data-sharing information systems as well as the cost to managed and maintain such systems and processes.

For this Plan for Change, note that DiMasi and colleagues are updating their seminal research on the time and cost for pharma R&D and plan to have it ready for submission in the Summer of 2013 (*personal communication*). Therefore, one proposal is to have a discussion of OSRD incorporated into their paper and/or collaborate on a companion paper.

3. Discussions with the executive team of PRA International in regards to appointing this researcher as PRA’s representative to TransCelerate, with the intent of using these research results to explore OSRD both within PRA and the broader TransCelerate consortium.

4. By 30 October 2013, a Business Plan will be presented to PRA’s Executive Management to create a Clinical Innovations Unit and forge links to similar units within pharma and CROs, academia, and with regulators.

5. Finally, as OSRD and other open innovations are starting to become discussed at conferences and forums, a presentation on these dissertation results will be submitted to the Disruptive Innovations 2013 meeting and/or to the Drug Information Association (DIA) Annual Meeting in June 2014.
This plan for change describes both the large scale, over-arching efforts required to innovate R&D, but also five steps proposed to be implemented before the end of 2013 to maximize dissemination, in a variety of venues, of these results.
Chapter 7: Discussion and Limitations

As with all research, this study is subject to limits and potential biases which can skew the results. First and foremost, this is an exploratory, qualitative study of expert opinions as whether OSRD could improve the quality and efficiency of pharma R&D. As discussed in the Methods section, key informant interviews are not intended to generate testable hypotheses in the statistical sense. Indeed, the purpose here was to seek informed opinions from several stakeholders to provide a foundation for future discussions and research. By design, this qualitative research cannot quantify the potential impact of OSRD on quality and efficiency. Therefore, modeling the economic impact of OSRD must follow in order to inform the debate over any financial advantages and disadvantages of OSRD.

Other limits exists both in the design of the study as well as its execution, including:

1) Design – Interviewer Bias: The majority of this interviewer’s career has been spent in industry, particularly CROs, thereby increasing the risk that the interviewer would be sympathetic to the current pharma R&D processes and therefore skew both the questions and interpretation of responses to benefit the status quo (i.e. less transparency and collaboration to protect business interests). One of the academic key informants voiced concerns about this potential bias, describing CRO employees as “vultures”. However, it is
reasonable to suppose that this interviewer would not have posed the research topic in the first place if biased against it. The interview questions were designed to encourage open responses to avoid biasing feedback either in favor of or against OSRD. Finally, verbatim quotes were cited throughout the results, with the intent to have the key informants views and context speak for themselves and not reflect a priori views of the researcher.

2) Execution – Interviewee Bias: It is possible that key informants would tend to answer in favor of OSRD, as that was the research topic, in order to be supportive of the research efforts. This bias may be characterized as people trying to be polite by simply saying what they think a researcher wants to hear. Moreover, it is possible that senior executives and regulators would not want to be publically noted as being against transparency and therefore might not speak freely. To minimize the risk of such bias, the list of key informants are confidential and their quotes are not attributed other than high-level role and stakeholder group. Therefore, key informants would neither gain from supporting OSRD nor be penalized for criticizing it, and therefore there would be little pressure to avoid candor.

3) Execution – Participant Sampling Bias: It is always possible that either through intent or accident that the participating key informants are not representative of the broad drug development community. To reduce this risk, the initial list of potential key informants included over 45 names and represented three important stakeholder groups: academia, industry, and regulators. At least three representatives were interviewed from each group,
with a weighting to industry as these key informants were pre-supposed to harbor the most critical views of OSRD concepts.

However, to further reduce the risk of sampling bias, this research would have benefited from non-US participants, as drug development is a global endeavor and effects global health. This option was considered but this was determined infeasible for the current effort.

Also, as discovered as part of the research results, payers such as insurance companies are becoming a key stakeholder group, and therefore including payers as key informants might have been instructive. Moving forward, it will be important to include payers in major discussions about pharma R&D innovations, OSRD or otherwise.

Finally, interviewing patient advocacy groups might have been instructive, and this is by far the most heavily invested stakeholder group not sampled. This option also was contemplated but not implemented as it was assumed that such groups would embrace transparency and collaboration without substantial reservations. However, this research does not validate this assumption.

4) Execution - Quality questions were ineffective: After interviewing the first five participants, it became clear that the questions about OSRD and quality were not interpreted by the key informants as intended. The goal of the quality question was “process quality”, whether OSRD would have a positive, negative, or neutral impact on the design of studies and interpretation of
results. However, many key informants interpreted the question to mean other important issues which this research was not designed to explore, such as drug developer “integrity” and “patient safety”. For the remaining nine interviews, an attempt was made to rephrase the quality questions specifically around study design and analysis, but nevertheless most key informants tended to discuss operational efficiencies rather than the quality of study designs and processes.

With each of these potential limitations and biases considered, the study results nevertheless support that transparency and collaboration such as that envisioned by OSRD would be positive for: 1) science, 2) patients as individuals, and 3) population health as a whole. It is not surprising that representatives from academia and the FDA embraced the concept of OSRD. However, it is remarkable that the industry executives interviewed generally believed that more transparency and collaboration would be advantageous, even perhaps financially. Furthermore, although serious concerns were raised that OSRD may be impractical to implement in the foreseeable future, these same key informants provided numerous examples (Tables 12 and 13) where OSRD-like concepts are already in place, albeit not widely known, and that the financial benefits of these initiatives are already being noted by pharma. This finding is critical, as it suggests that industry is trending toward becoming a proponent of OSRD-like efforts, ready and willing to lead as opposed to resisting transparency “kicking and screaming” with “a fleet of lawyers throwing themselves on the Capitol steps” of Congress, in the words of two key informants.
This raises the question whether any savings, from OSRD or any innovation, would be passed on to consumers or held by pharma to increase profits. While it is impossible to predict what a business or industry might do in the future, there are potential forces that might dissuade pharma from simply retaining any savings. First, OSRD as proposed by this research includes some sharing of financial information around R&D costs and efficiencies. Therefore, if OSRD were successful in reducing costs and pharma used that to increase net profits, such actions would be visible to the public and likely become another public relations problem for an industry that is already widely mistrusted. Second, CER and reimbursement reform as discussed in the Introduction is likely to put downward pressure on profits, and therefore OSRD or other process innovations may be a way for industry to offset profits lost due to reimbursement actions by public and private insurers. In other words, pharma may be compelled to consider OSRD to mitigate decreased profitability, but not increase margins.

While the proposed OSRD paradigm was largely supported by the key informants, a detailed framework for exactly what is shared with whom and when, in what forum or format, remains to be explored and codified. And although the work to carefully define the specifics of OSRD remains, this research uncovers a nascent consensus that more transparency and collaboration is inevitable and potentially positive. As proclaimed by Thomas Krohn (not a key informant), the head of Eli Lilly’s Open Innovation Unit:

“It isn’t a question IF change is happening, it is what will pharma do in light of it. We are committed to open innovation in clinical research. We look forward to enabling and collaborating with others to accelerate clinical research and greater meet patient needs.”

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If more transparency and collaboration is inevitable, then is OSRD a possible solution to the problem of high costs for pharmacotherapy and the resulting negative impact on population health? These study results support that transparency and collaboration such as that envisioned by OSRD would be positive for: 1) science, 2) patients as individuals, and 3) population health as a whole. This finding perhaps is not remarkable. However, OSRD could also be positive for the pharma industry in terms of public relations, efficiency and costs. This finding has the potential to have a revolutionary impact on the way that drugs are researched, reported, and approved, with the possibility of both maintaining pharma profitability while reducing the costs of pharmacotherapies to consumers, worldwide.
Appendix 1: Introductory Letter for Potential Key Informants

Note: May be provided to potential key informant by mail or e-mail, or read as a telephone script and then provided later by mail or e-mail.

[Date]

Dear [insert name],
My name is Timothy King, and I am a Doctoral Student and the University of North Carolina in Chapel Hill. I am working on dissertation research as part of requirements to obtain a Doctorate of Public Health in Health Leadership. [Note: If one of the Dissertation Committee members recommended a potential Key Informant, then the following sentence would be included – [DissComm Name] suggested that I contact you.]

My dissertation topic is the exploration of potential innovations in pharmaceutical research and development (R&D), with a particular focus on recent efforts referred to as “Open-Source”, “Open-Science”, or “Crowd Sourcing” R&D. A basic element in Open-Science R&D (OSRD) is more transparency between pharmaceutical developers and regulators, and perhaps between academia, competing pharmaceutical companies and the broader public.

Generally, OSRD approaches are limited to rare (“orphan”) conditions, or Neglected Tropical Diseases, but my research explores whether it could have broader applications and benefits in mainstream pharmaceutical R&D.

If you are interested in learning more about this research and perhaps participating in a confidential interview, please review the attached brief description of OSRD. Then, if you agree, we can schedule a convenient time for a 45-60 minute interview.

Please let me know if you have any questions.

Kind regards,

[Signature]

Timothy King
Doctoral Student
University of North Carolina, Chapel Hill
kingtdn@unc.edu
+1 919.597.9060

Biographical Sketch
Mr. King has managed and directed clinical device and drug development globally since 1990. This includes director and executive-level responsibilities for interventional (drug and device) and observational studies. Recent experience includes being the Vice President for Clinical Operations at a biotech firm, and directing project management staff in the Global Cardiovascular, Diabetes and Late Stage Trials group for a large contract research organization (CRO). His CRO group was responsible for over 20 Phase I to IV trials for drugs, biologics, devices and diagnostics in over 40 countries with a total budget in excess of 300M USD labor. Before this he was the Head of Infectious Diseases and General Medicine at a large Academic Research Organization (ARO). At the ARO, he led a group of 55 project managers, monitors, and assistants and was responsible for resourcing for the 225-person Clinical Operations group. He holds a Masters degree in epidemiology and is now pursuing his Doctorate in Public Health.

Dissertation Committee

John Paul (Chair), Margaret Dardess, Don Holzworth, Christopher Shea, John Vernon, Bryan Weiner
Appendix 2: Hypothetical Model for Open-Science in Pharmaceutical Research and Development

Note: The intention is to provide this brief synopsis to potential Key Informants along with the Introduction Letter in Appendix 3.

Open-Science Research & Development (OSRD)

Pharmaceutical companies are beginning to explore broader collaborations and transparency with each other, particularly in R&D for Neglected Tropical Diseases (NTD) and Orphan indications. These efforts are called by some Open-Science (OSRD), loosely modeled on “open-source” software development. Please consider this 30 January 2012 press release from the Drugs for Neglected Diseases initiative (DNDi), where 11 major pharmaceutical companies are co-investing $785 million to support R&D efforts:

“In the largest coordinated effort to date to combat NTDs, the group announced… that they would… share expertise and compounds to accelerate research and development of new drugs… Partners also… pledged new levels of collaborative effort and tracking of progress.”

Another example from Wall Street Journal (Rockoff & Winslow, 11 July 2011):

“Scientists also had to keep their work secret, exploring new medicines without insight from outsiders. But companies can’t keep a tight leash on their researchers if they expect to capitalize on the deepening understanding of how diseases happen, contends the chief executive of Sanofi SA, Christopher Viehbacher.”

The premise here from industry is that more transparency and collaboration in R&D reduces timelines and costs. Some academic proponents of OSRD for NTDs go further than broader collaborations and advocate for sharing drug discovery information publically via the internet for anyone to use. Both industry and academia assume that there is little or no profit in new drugs for NTDs and therefore any loss of competitive advantage is irrelevant.

However, reducing R&D timelines and costs are very important for all drug development, where each new drug requires on average $1 billion or more and 12-15 years for approval. Therefore, my research explores whether OSRD might have broader applications beyond NTD and Orphan drugs. Can OSRD or components of it be modified and applied to all drug development to improve efficiency and quality but not undermine profitability?
Hypothetical OSRD Approach (for discussion purposes)

To preserve a patent-based, for-profit model, presumably the molecule and methods for synthesis and manufacturing would remain proprietary to the company holding the patent. Therefore, drug developers would still have a product to sell if approved. Also, in blinded clinical trials, study results would not be broadly divulged until after un-blinding to avoid introducing bias.

Beyond that, proprietary information that might be shared during the R&D process could include:

- Laboratory discovery process data
- Pre-clinical (animal) research data
- Phase I-IV clinical research data
- Clinical Development Plans including Study Protocols
- Targeted Product Profiles
- Some or all correspondence with regulators
- Costs related to R&D, manufacturing, marketing and distribution

Under an OSRD approach, key questions include exactly what information might be shared, with whom, and when? If you agree to be interviewed, consider the impact of more transparency and collaboration on drug development beyond NTD and Orphan drugs.
Appendix 3: Informed Consent Form (for Verbal Consent)

Verbal Informed Consent Form for Interviews about Innovations in Pharmaceutical Research and Development

DrPH Dissertation Research Project

Timothy King
Doctoral Student at the
University Of North Carolina, Chapel Hill

Version: 30 May 2012

You are being asked to take part in a research study examining the opinions and attitudes of various people involved in pharmaceutical research and development (R&D). This includes one-on-one interviews about potential innovations in pharmaceutical R&D, in particular recent proposals for an “Open-Science” approach to R&D (OSRD). Your participation in this study is voluntary. You may refuse to participate or you may withdraw your consent during the interview and it will stop.

Details about this study are discussed below. You will be given a copy of this consent form. Please ask any questions you have about this study at any time.

What is the purpose this study?

The purpose is to learn more about peoples’ opinions and attitudes regarding innovations in pharmaceutical R&D, particularly OSRD.

How long will your part in this study last?

Your participation will last about one hour.

How many people will take part in this study?

About 15-20 people are expected to participate in this study. Participants will be invited to join the study from several groups involved in pharmaceutical R&D including academia, industry, and regulatory groups.

What will happen if you take part in the study?

Prior to the interview, you will be given a brief description of an OSRD model to inform your thoughts and answers. There are no right or wrong answers to the
questions that will be asked. You may choose to respond or not respond at any point during the discussion. The interviews may take place either by telephone, video conference or face-to-face, and you can choose which format you prefer.

**Audio Recording**

Only if you agree, the interview will be audio taped so that we can review your responses to make sure we understand what you have said. Even if you agree to be recorded at the beginning of the interview, you may ask us to stop recording at any time.

**What are the possible benefits from being in this study?**

No. You will not receive any direct benefit from this study.

**What are the possible risks or discomforts involved from being in this study?**

We do not anticipate any significant risk or discomfort to you from being in this study. One risk is that comments you share and which you would not like to be shared with others could be shared by accident. To prevent this from happening, we will keep everything you say confidential, we will not store your name with any audio recordings or transcripts, and we will not refer to you by name or institution when we write up the results of the interviews. All audio files will be kept in locked cabinets or secure servers throughout the study and will be destroyed when the study is completed. Therefore, we encourage you to be as honest and open as you can, yet remain aware of our limits in protecting confidentiality.

**Will you receive anything for being in this study?**

No. You will not be given anything for participating in this study.

**Will it cost you anything to be in this study?**

No. The only costs to you are your time.

**What if I am a UNC employee or student?**

Taking part in this research is not a part of your job or being a student, and refusing to take part will not affect your standing in your job or your status as a student.

**What if you have questions about this study?**

You have the right to ask and have answered any questions you may have about this research. If you have questions or concerns, you should contact Timothy King, DrPH Student (919-597-9060; kingtdn@unc.edu). He is the leader of this project and will be happy to answer your questions.
Also, you can contact Timothy’s Dissertation Committee Chair, John Paul, PhD (919-966-7373, john_paul@unc.edu) with any questions or concerns you may have.

**What if you have questions about your rights as a research participant?**

All research on human volunteers through UNC has been reviewed and approved by a committee that works to protect your rights and welfare. If you have questions or concerns about your rights as a research subject you may contact, anonymously if you wish, the Institutional Review Board at the University of North Carolina, Chapel Hill, at 919.966.3113 or by email to IRB_subjects@unc.edu.
Appendix 4: Key Informant Interview Guide

Interview Format

Key informants will receive a written invitation to the study and a brief description of OSRD (Appendices 3 and 4) prior to the interviews. If participants agree to be interviewed for the study, I will schedule in advance a convenient time when we can talk privately either in-person, via web conference, or by telephone. It is critical that I (the interviewer) be neutral, so that the key informant is at ease and can respond to questions candidly and without influence.

I will confirm the key informants' verbal informed consent to participate at the time of the interview, prior to any data collection, including a request to audio record the discussion for later transcription. The questions (Appendix 6) move from general to specific as follows:

- **Opening**: Confirm verbal informed consent for both the interview itself and audio recording.

- **Introductory**: A broad question to determine whether the key informant believes that the current drug discovery and development approach is acceptable, or whether there is need for innovation. A follow-up question will assess their current awareness of open-science/open-source/crowd sourcing in R&D.

- **Key Questions**: The questions that directly address the study’s key research questions; and
- **Ending**: A request to clarify any information from the interview.

The interview will conclude with a thank you and request for permission to contact her/him in the future if additional questions or need for clarification arises.

Finally, immediately after the interview or as close to it as feasible, I will review and expand upon my notes. I will also make a qualitative appraisal of the interview, assessing the following from my perspective as the interviewer:

- **Interview “tone”**: Did I feel that the key informant was engaged? Was the tone cordial, distracted, antagonistic, etc.?
- **Interview length**: Was the time adequate for full discussion of each key question?
- **Clarity**: Did the key informant seem clear on the proposed OSRD approach (regardless of whether s/he seemed to accept or reject the approach)?
- **Direction**: Did the key informant generally answer the questions as asked, or tend to veer off topic and need to be re-directed?
- **Veracity**: Did I have the impression that the key informant spoke candidly? Did s/he appear comfortable to be able challenge or disagree with the proposed OSRD approach?
Appendix 5: Key Informant Semi-structured Interview

Note: This Interview may be conducted face-to-face or by telephone.

General Demographic and Background Information

I plan to gather much information on the key informants degree(s), roles, overall experience, etc. prior to the interview and simply ask them to confirm it. This will allow me to align each key informant with the appropriate stakeholder group (industry, regulatory, academia). This information will not be used to identify the informant in the dissertation paper. Such information will include:

   a. Major roles in medical R&D (e.g. clinical researcher, “bench” scientist such as biochemist or molecular biologist, statistician, etc.)

   b. Years of experience in drug discovery and development, medical diagnostic and/or device R&D

   c. In what settings (e.g. academia, pharma, biotech, CRO, regulatory agency, insurance company)

   d. Education and training (both degrees and field of study)

   e. Demographics (sex, age, race, etc.)

Introduction and Verbal Informed Consent

Note: Confirm that verbal informed consent is given prior to beginning interview and/or audio recording.
I am Timothy King, a student in the Doctor of Public Health Program at UNC-Chapel Hill. The information I collect is for my dissertation research and is confidential. Within the dissertation you will not be identified (by name, title, or institution).

Please let me know if we can begin the interview and whether I may record our conversation. [If Yes, then] Please let me know if you want me stop the recording at any point in our interview.

[If verbal consent granted, then]

Thank you for agreeing to participate in this interview to discuss innovations in pharmaceutical research and development (R&D), in particular the concept of open-science drug research and development (OSRD).

Interview Questions

1. **Main Question:** What are your thoughts on the current process for drug R&D in terms of quality and efficiency?

Potential Follow-up Questions:

- Please describe your understanding or impressions on Open Science R&D approaches for orphan diseases and/or NTDs.

- How do you define quality? Efficiency?

- Prompt KIs to respond in terms of the various categories of issues -- e.g. scientific, regulatory, legal, policy, financial, operational, business development such as in- or out-licensing, etc.
Now, in considering the hypothetical OSRD approach… (note: refer the key informant to the brief OSRD description in Appendix 4 for the remaining questions as needed)

2. **Main Question:** Would OSRD, implemented more widely than just for orphan conditions/neglected tropical diseases, have a positive, negative, or neutral impact on the **quality** of clinical research design, conduct, analysis, and results overall?

*Potential Follow-up Questions:*

- How do you define quality?
- Please elaborate on any impact on research design/conduct/analysis/results.
- Prompt KIs to respond in terms of the various categories of issues -- e.g. scientific, regulatory, legal, policy, financial, operational, business development such as in- or out-licensing, etc.

3. **Main Question:** Would OSRD, implemented more widely than just for orphan conditions/neglected tropical diseases, have a positive, negative, or neutral impact on the **efficiency** (time and/or costs) of clinical R&D overall?

*Potential Follow-up Questions:*

- How do you define efficiency?
- Please elaborate on any impact on research conduct (operations).
• Prompt KIs to respond in terms of the various categories of issues -- e.g. scientific, regulatory, legal, policy, financial, operational, business development such as in- or out-licensing, etc.

4. **Main Question:** What might a broadly adopted OSRD approach look like?

**Potential Follow-up Questions:**

• Are there components of the proposed OSRD approach with which you disagree? [Note Appendix 4 for types of information that might be shared]

• If so, should they be deleted or modified? Please elaborate. Prompt in terms of discovery, pre-clinical and/or clinical information.

• Are there components that should be added, that is, more kinds of information shared?

• What about the timing of sharing information, such as on-going (“real time”), or waiting until certain conditions are met? If so, what conditions.

5. **Main Question:** What would be barriers to a broader implementation of an OSRD approach to more mainstream pharmaceutical R&D?

**Potential Follow-up Questions:**

• Prompt KIs to respond in terms of the various categories of issues -- e.g. scientific, regulatory, legal, policy, financial, operational, business development such as in- or out-licensing, etc.
6. **Main Question:** Discussions about OSRD are essentially about innovating and improving clinical research. Are there other and potentially better innovations that should be considered?

**Potential Follow-up Questions:**

- Prompt KIs to respond in terms of the various categories of issues -- e.g. scientific, regulatory, legal, policy, financial, operational, business development such as in- or out-licensing, etc.

Note to Interviewer: Briefly ask the interviewee if there are any additions, deletions, or clarifying comments they wish to make. Time permitting, confirm your notes on each question to ensure you have correctly understood the interviewee's comments.

**Interview Conclusion**

Thank you for your time today to discuss Open-Science R&D. This has been very helpful to me and my doctoral research. If you have any additional thoughts or questions, please contact me. Also, may I contact you in the future if I have follow-up questions? [Note **YES** or **NO**]. Finally, if you are interested, I would be happy to share the results of my research when the final report has been approved and accepted by UNC (expected 2013). [Note **YES** or **NO**].
Appendix 6: IRB Review

To: Timothy King
Health Policy and Management
3112 Chelmsford Drive, Durham, NC 27705

From: Office of Human Research Ethics

Date: 6/04/2012

RE: Notice of IRB Exemption
Exemption Category: 2. Survey, interview, public observation
Study #: 12-1033

Study Title: Pharmaceutical Research and Development: A Key-Informant Assessment of Whether an “Open-Science” Model Could Improve Clinical Research in Terms of Quality and Efficiency

This submission has been reviewed by the Office of Human Research Ethics and was determined to be exempt from further review according to the regulatory category cited above under 45 CFR 46.101(b).

Study Description:

Purpose: Determine whether an "Open-Science" model for commercial pharmaceutical development (R&D) is feasible and desirable, where Open-Science is defined as modifying the current R&D process to be more transparent via providing development plans, protocols, and data proactively and easily for public review.

Participants: Approximately 25 key informants from several key stakeholder groups, namely academia, industry, and regulators.

Procedures (methods): Key informant interviews, either face-to-face or via telephone/web-conference. Permission to record and transcribe will be sought via verbal informed consent.

Investigator’s Responsibilities:

If your study protocol changes in such a way that exempt status would no longer apply, you should contact the above IRB before making the changes. The IRB will maintain records for this study for 3 years, at which time you will be contacted about the status of the study.

Researchers are reminded that additional approvals may be needed from relevant "gatekeepers" to access subjects (e.g., principals, facility directors, healthcare systems).

CC: John Paul, Health Policy and Management
Appendix 7. Coding Manual for Interview Transcripts

26 December 2012

References

Miles MB, Huberman AM. Qualitative data analysis: An expanded sourcebook. 2nd Edition. Sage Press (1994)


General Notes

- Participant code = first letter of last name plus order that interviewed confirmed (e.g. If Jane Doe was the third person to confirm a date/time for an interview, then her participant code is D3)
- Interviewer’s questions/comments not coded.
- Basic demographic information – not coded, but summarized in tabular form. Equivalent to “Attribute” coding in Saldaña
- Magnitude Coding – most questions were semi-structured and intended to solicit broad or “open” responses, not one-word or “closed” responses. Questions #2 and #3 asked respondents to state whether they thought something was “positive, negative, or neutral” overall, and then describe why.
- Structural/Descriptive/Provisional Coding. The main structure of codes, and then ultimately the “themes” were to a large degree pre-identified during the study design stage and embedded in the questions asked. However, additional codes and themes were required to handle unanticipated data in interview responses.
  - A priori structural codes included Study Operational “Quality”, “Efficiency” in terms of “Time” and also “Costs, “OSRD” approaches, “Transparency”, “Barriers” to OSRD and/or “Other Innovations”
  - Also prompted participants to respond to questions within certain “buckets”, specifically scientific, regulatory, legal, policy, financial, operational, business development
  - In vivo (“verbatim”) codes were identified and used when possible, although most participants tended to use the key terms as they were stated in the interview questions.
- Process Coding: These were all one-to-one semi-structured interviews, not in an otherwise interactive environment. Therefore, the only process codes came from the brief assessment the interviewer conducted after each interview. In that post-interview assessment, I commented on the “tone”,

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“length”, “clarity”, “direction” and “veracity” of the interview. These were not coded, and no other coding of process was conducted.

- Affective/Emotion Coding: Most interviews were professional, formal or scholarly in tone, with little emotion shown. However, wherever emotion or emphasis was exhibited, I noted in the transcriptions by underlining the transcribed text.
- Versus Coding: Many participants were willing to play “devil’s advocate”, where they would comment at length on concepts or issues with which they previously disagreed, either wittedly or un-wittedly. I noted this in the transcript coding with the term “versus”.
- Administrative: I used red text to note areas of the transcripts where I wanted to re-check the recording to verify the transcript, and yellow highlighter to note quotes I would like to explore further to include verbatim in the results and discussion.

<table>
<thead>
<tr>
<th>Code</th>
<th>Type</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality</td>
<td>Descriptive</td>
<td>In terms of study operational “quality”, also data quality, although some interviewers grouped “patient safety” issues into discussions on quality</td>
</tr>
<tr>
<td>Efficiency/Time</td>
<td>Descriptive</td>
<td>Positive/Negative/Neutral impact on time it takes to move drug candidates through R&amp;D process, and related discussions</td>
</tr>
<tr>
<td>Efficiency/Costs</td>
<td>Descriptive</td>
<td>Positive/Negative/Neutral impact on financial cost it takes to move drug candidates through R&amp;D process, and related discussions</td>
</tr>
<tr>
<td>OSRD approaches</td>
<td>Descriptive</td>
<td>Discussions about what information should/should not be shared in OSRD approach, and when</td>
</tr>
<tr>
<td>Transparency</td>
<td>Descriptive</td>
<td>References the “transparent” sharing of information, data, and/or regulatory feedback, etc.</td>
</tr>
<tr>
<td>Barriers</td>
<td>Descriptive</td>
<td>Barriers to adopting innovations, OSRD in particular</td>
</tr>
<tr>
<td>Timing</td>
<td>Descriptive</td>
<td>Comments on the best timing of sharing information (e.g., after drug approval, “real” time, etc.)</td>
</tr>
<tr>
<td>Code</td>
<td>Type</td>
<td>Notes</td>
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<tr>
<td>Innovations</td>
<td>Descriptive</td>
<td>When participants reference innovations other than OSRD</td>
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<tr>
<td>Scientific</td>
<td>Descriptive</td>
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<tr>
<td>Regulatory</td>
<td>Descriptive</td>
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<td>Legal</td>
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<td>Policy</td>
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<td>Financial</td>
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<td>Operational</td>
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<td>Business Development</td>
<td>Descriptive</td>
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<tr>
<td>Decision making</td>
<td>Descriptive</td>
<td>Discussion about how decisions get made, and whether transparency/collaboration can improve decision making</td>
</tr>
<tr>
<td>Ethical concerns</td>
<td>In vivo</td>
<td></td>
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<tr>
<td>Evidenced-based medicine (EBM)</td>
<td>In vivo</td>
<td>Really an innovation, but one that decreases efficiencies?</td>
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<tr>
<td>Market Access</td>
<td></td>
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<tr>
<td>OSRD-like examples</td>
<td>In vivo</td>
<td>Participants who gave examples where OSRD has already happened, is happening. E.g. Gordon conferences, HIV collaborative effort, SNiP consortium, DNDi, TransCelerate</td>
</tr>
<tr>
<td>Patient safety</td>
<td>In vivo</td>
<td></td>
</tr>
<tr>
<td>Payers</td>
<td>In vivo</td>
<td>Discussions of reimbursement, be it by private insurers, Medicare/Medicaid, individuals, etc.</td>
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</table>
### Appendix 8: Results. Additional Key Informant Comments on the Efficiency of Current Pharma R&D Process, in Terms of Time and Costs

<table>
<thead>
<tr>
<th>Quotes: Efficiency of Current Pharma R&amp;D Process</th>
<th>Participant Role</th>
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<tr>
<td>The [R&amp;D] process works fine relative to if the ability to protect trade secrets but on the other hand, I think the industry recognizes the process is very costly and requires not only enormous investment in financial resources but also in time. But it certainly has been designed around the premise of importance to protect trade secrets.</td>
<td>CEO, CRO</td>
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<td>Well, it's very slow, I think…There is probably not enough communications between the commercial side by which I mean expressions of demand for a product and scientific discovery. So, you end up with some drugs or forms of drugs developed that never really come to market or meet a demand. Costs are ungodly.</td>
<td>VP, Large Pharma</td>
</tr>
<tr>
<td>Now, efficiency - completely different grade completely different answer. There obviously different models that companies, and I guess you have to look at this from the standpoint of a commercial enterprise because that's how most drugs make it into use, but there are obviously many models that companies employ to get drugs from discovery through registration and some clearly work better than others. The marketplace tends to wash out those that don’t do it as efficiently as they should, but even with that caveat I think overall, the drug development process is an inefficient one. And I would grade it somewhere in the 50 – 60% range.</td>
<td>CMO, CRO</td>
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<tr>
<td>The current process is cumbersome, hard to navigate at the FDA…</td>
<td>CEO, Small Pharma</td>
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<td>Clearly, there’s been this concern in the industry around patent-cliffs… Companies have not been able to replace their blockbusters with new products so one of the things they’ve done is merge, big horizontal mergers, as well as purchase smaller companies that are discovery oriented. For the most part the big horizontal mergers have not helped at all efficiency. In fact, I feel they could be a drag because there’s a big transition process, etc. I think there’s more rationale for some of the alliances that turn into mergers or acquisitions. Those might be helpful towards the process. So that’s the big picture.</td>
<td>Academician</td>
</tr>
</tbody>
</table>
### Quotes: Efficiency of Current Pharma R&D Process

<p>| Basically coming down to the question of “well what about the development process?” The clinical side of it keeps getting longer. Well, not so much longer, but costlier and poorer success rates. So, that’s a big concern. |  |
| Well, it’s failing. It’s failing because we’re not getting very many new molecular ideas. We’re getting a lot of “me too” drugs. The cost of bringing drugs to market is continuing to escalate, and so what we have is the traditional model for drug development is increasingly ineffective. | Academician |
| I think at some level there are problems in both (Drug Discovery and Development]. Discovery since the industry has moved to this in-licensing model, the issue there is kind of this valley of death between academia and biotech and Pharma where there’s not a lot of money going into moving things forward. So, that’s one series of questions and challenges: are there ways in which we can enhance discovery, people share science readily anyway, getting the proof of concept if fundable, it’s going to be an increasing issue. That’s a critical issue. What are the milestones and are there really commercially viable milestones? So, that’s some of the discovery issues. A development issue is it’s always way too costly. You brought up, it’s too costly and the development side for small market molecules, that’s both on the development side and I should say on the marketing side. You know, if you can’t reach your target audience in an economically viable way. So, I think there is some of both in there. Then, the other issue underneath all that, the value of the information you are getting, where you have global clinical trials, how does that help inform decisions in any specific market even for approvable reimbursement. No, it’s definitely not working. I think there are some encouraging signs out there so if you look at some of the growth indicators like number of new drugs approved especially new molecular entities for priority indications after the big down turn in the 2000’s that’s starting to pick back up and showing signs of further improvement, but it’s still very costly and over time it’s gotten much more costly and more time consuming to bring more drugs to market and while it has been major revision over the past decade in how Pharma companies and biotech companies are doing in investment and R&amp;D with an emphasis on genomics and more target | FDA, Senior Official |
|  |  |  |</p>
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<tr>
<th>Quotes: Efficiency of Current Pharma R&amp;D Process</th>
<th>Participant Role</th>
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<tr>
<td>therapies and not just filling in, it’s still hardly what anyone would view as optimally productive and I think that’s reflected in some real challenges and venture capital investments and other private investments in R&amp;D in the area going down.</td>
<td>FDA, Senior Official</td>
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<tr>
<td>No, I mean, it’s terrible because it’s so costly and they have such poor success rates – the predictability of their models are so bad that the enterprise has been endowed until recently.</td>
<td>FDA, Senior Official</td>
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## Appendix 9: Results. Additional Key Informant Comments on the Effect of OSRD on the Quality of R&D

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<tr>
<th>Quotes: Effects of OSRD on the Quality of R&amp;D</th>
<th>Participant Role</th>
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<tr>
<td>I think there’s a lot that could be done on the process side and there are lots of initiatives moving right now at different places. TransCelerate which we talked about as the latest of these, but in the process innovation area you had down, in the last ten years as in the Critical Path Institute it has the FDA as kind of a grandfather organization that works with them and it’s focused on predicting safety tests.</td>
<td>Academician</td>
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<td>[If when you say] quality, you mean more information that would lead to better decision making or better outcome, the answer would be yes. I don’t know if it would improve the quality of the study from the perspective of data quality, but certainly more info is always better than less.</td>
<td>CEO, CRO</td>
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<td>Positive, definitely positive… Because if it's open, it’s disclosed to virtually everybody to look at. You have an automatic check on what you are doing. And you probably are much more careful… with your own quality controls if it’s open.</td>
<td>VP, Pharma</td>
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<td>So this whole idea then if I understand this if we were to create a pathway or venue for doing open science, open pharmaceutical science… would that produce a higher quality? I don’t know. The answer is no because I believe that the quality has to be built into the system from the integrity point of view. Would it impact integrity? I don’t think so because the regulations are really highly defined and the punishment for an IND sponsor would be immense if the integrity issues were in some way violated. So I don’t think it would make an effect on so-called quality at least as I define it.</td>
<td>VP, Pharma</td>
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<td>I think that the impact on quality would be neutral, in terms of research design, conduct, analysis, and results… those terms seem more related to efficiency than quality.</td>
<td>President, CRO</td>
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<td>I guess my knee-jerk reaction to that is that it would depend on which transparency was being exercised and the dimension on which it’s being exercised. To a degree, I think you can point to the scientific literature as the traditional vehicle for dissemination of information. Advances in science as conveyed through the scientific</td>
<td>CMO, CRO</td>
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<td>Quotes: Effects of OSRD on the Quality of R&amp;D</td>
<td>Participant Role</td>
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<td>literature, and by that I mean the publications and presentations tend to drive innovation across the enterprise. Now what you’re talking about is transparency beyond that. The question that I guess you’re asking is would there be incremental additive value in quality, and I’m sure ultimately efficiency would be the next logical question because of that and I think you’d have to hypothesize that there would be incremental value. At what point do the owners of proprietary information share the data and presumably it’s shared at some point, when it becomes not a commercial advantage to hold on to it any longer and it’s to the advantage of the individual in the corporation to further their own careers through publication and so on. It becomes more widely disseminated and so what you’re basically talking about is sort of moving the timeline for quality improvement or enhancing efficiency in one direction or another by becoming more transparent sooner rather than later. So, I think based on the current paradigm, you’d have to conclude that more transparency earlier would result in improved quality and improved efficiency, but how do you quantify that, can you quantify that? I don’t know.</td>
<td>CEO, Small Pharma</td>
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<td>It would potentially be a positive, but there are many challenges to a broader implementation. My feeling is that it has to be proven several times in the orphan arena to establish best practices and allow it to migrate more naturally to the larger indications like diabetes (which has been fraught with many problems).</td>
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<td>Part of the reason drugs fail in phase III is simply that phase II is inadequate. Wrong dose, wrong study endpoints, and inadequately powered trial. That’s done all the time and it’s not quite clear to me how this transparency would actually help that.</td>
<td>CEO, Small Pharma</td>
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<td>Well I don’t see how it could possibly be adverse. How much help it would be is hard for me to say, but you’ll always learn from adverse experiences. I think everyone does. I can’t help but think it would be useful for people to see other people’s experiences; especially adverse experiences. So, I think it would be useful, how revolutionary it would be, that’s harder to say.</td>
<td>Regulatory</td>
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<td>So, for everyone who’s working in a particular clinical area, it’s in their interest to validate whether there are good early markers of both clinical benefit but you don’t have to do</td>
<td>Regulatory</td>
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<tr>
<td>Quotes: Effects of OSRD on the Quality of R&amp;D</td>
<td>Participant Role</td>
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<td>quite so long of a trial to get the outcome and safety risk of products in particular patients and the reason that has to be open science is that only one company is going to have a limited amount of data that could be used to do those validation studies in order to predict a marker is really a valid indicator and because just from one company there’s going to be FDA concern that this is not replicable or the company has a specific vested interest in showing that it was their compound that they intend to use the marker for is safe and effective. Whereas if it was a pooled effort, it’s much more convincing that what you’re finding is true, scientifically valid conclusion. And then similarly having a sort of shared mechanism for developing further evidence on the safety and maybe effectiveness of treatment. So, definitely safety in the post market setting, which could be shared, shared infrastructure. We’re working on a project that does this called the Sentinel Initiative with the FDA, which involves support from companies who are working with a range health, and electronic record systems with shared data on safety surveillance, which again applies to a specific product of each company. Ones that they would normally be studying in their own phase IV study which would involve some proprietary investment and is instead being done through a shared, common infrastructure which is lower cost, easier to use, easier to get large numbers on, easier to reach definitive conclusions about. Those are several areas where I think there’s real potential.</td>
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## Appendix 10: Results. Additional key Informant Comments on the Effect of OSRD on the Efficiency of R&D

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<tr>
<th>Quote: Effects of OSRD on the Efficiency of R&amp;D</th>
<th>Participant Role</th>
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<tr>
<td>So I think in process innovation, open source can be very valuable and consortia of various kinds. Open source clearly can be very profitable at a very early stage, very useful, fruitful at a very early stage. That is at early discovery stage. I think it could be significant, just like, I’m [referencing] the cost study, you know the cost of R&amp;D with DiMasi and his group. You know if you can cut down a year, it has a significant impact. If you can reduce the cost. I think it’s not a very efficient process, the way big Pharma goes about it. They have huge regulatory groups and they work with others, CROs, etc. They’re very risk averse, they do more, they often do it in an inefficient way. Maybe some of this is for marketing, but it seems like the size of clinical trials are just getting bigger and the end success rate is getting lower. So I think there’s a lot that could be done to speed up the process and also to make it more targeted so I think you wouldn’t [need to] decrease cost by 50%, but if you could decrease cost by 20%, that’s a couple hundred million dollars.</td>
<td>Academician</td>
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<td>I can’t imagine that it would because in fact what now happens is every new case of drugs that comes along there are congeners in development that are often a year or two behind the original drug. So, the amount of time that a company has exclusivity on a class is relatively short. Take the DPP-4 inhibitors for diabetes. Sitagliptin was out for a year or two and then along came Saxagliptin and now there are 3 or 4 others emerging as well. So that saving trivial amount of money a couple hundred million dollars saved is nothing. Literally nothing in a multi-billion dollar market industry like this. So, I can’t see how it would ever be in an industry’s interest to share.</td>
<td>Academician</td>
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**Quote: Effects of OSRD on the Efficiency of R&D**

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<tr>
<th>Effects of OSRD on the Efficiency of R&amp;D</th>
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<td>…solving the challenges of designing the protocols and collecting the data and that kind of stuff? I know people have treated it as proprietary in the past, but to some extent that’s a farce. So, maybe being explicit about that. And on top of that, this idea of confidentiality is getting in the way all over the place. I know it’s not enforceable, people have these confidentiality agreements that just aren’t enforced, but legally you’re a risk in all kinds of ways.</td>
<td>Academician</td>
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<td>[Interviewer follow-up question: Do you think [OSRD] would be beneficial? Or do you think it’d be neutral or are there sort of unintended negative consequences?]</td>
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<td>I think if you make an argument that you’re already sharing data and you’re pretending you’re not, and then you just have all the downside of information and data sharing. So, maybe if we went to the other extreme, to some extent you should only have upside, right? Whatever negative impact information sharing can have it should be out there already.</td>
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<tr>
<td>…more information that would lead to better decision making or better outcomes, the answer would be yes, …certainly more info is always better than less. It would change initial study design because the more information available of a particular class of drugs that was similar be the case for across the industry. Yeah it would probably change the study design presumably with reduced the number of studies or number of patients required for the study. It would definitely speed the process.</td>
<td>CEO, CRO</td>
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<td>[Interview follow-up question: If it did speed the process up do you think that could have a positive impact on reducing the cost of developing drugs?]</td>
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<td>Yes, yes I believe so, yes.</td>
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<td>Well, if the regulators are involved earlier, then any issues are going to be apparent earlier and can be dealt with. I would think that that would be a positive… Because everybody working on the same therapeutic area can learn from each other’s mistakes and advances… If what you can come out with looking at specifically the [OSRD] orphan drug model and how it’s working there is are there some incremental things you can get from this that would speed up efficiency rather than changing the process wholesale, then you’ve really accomplished something.</td>
<td>VP, Large Pharma</td>
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</table>
**Quote: Effects of OSRD on the Efficiency of R&D**

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<th>Quote</th>
<th>Participant Role</th>
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<tr>
<td>To look at this at a 10,000 foot level would it be possible that an open science type context would create a vision that companies could use collaboratively to help regulators and payers to really understand the direction of the evidence based medicine process. The answer to that is, yes, I do think it would be beneficial if the open science resulted in a collaborative enterprise that addressed some of these emerging issues. Especially the changes in regulatory science towards evidence based medicine and the effects of payer-reimbursement on the overall development process.</td>
<td>VP, Large Pharma</td>
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<tr>
<td>I think that across the broad spectrum it would have to add value because I think the open science concept would configure itself in such a way as collaboration occurred to create the most efficient cost-effective process that maintains the integrity quality of the ultimate deliverable. So, I think in that point of view, the open science would have at least the capability of having an improvement.</td>
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<td>[Interviewer follow-up question: Do you have any specific thoughts of where you would see the potential for improvements in an open science model in time and/or costs?] They would involve the planning and conduct of large epidemiological studies that define the frontier of evidence based medicine in some of these new emerging therapeutic areas. It would also be applicable in the context of having regulatory guidance that was consistent and supportable from both sides of the sponsor and the regulators that would have the highest level of efficiency and information access. So I think those two areas would be very applicable to the open science concept.</td>
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<td>[The impact of OSRD on efficiency] would be positive, in terms of the benefit of learning from each other.</td>
<td>CEO, CRO</td>
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**Quote: Effects of OSRD on the Efficiency of R&D**

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<th>Now on the efficiency side, it’s hard to argue that it wouldn’t be more efficient. The more information one has to consider in making your own decisions about the most efficient/cost effective and resource effective pathway to get to the end zone, the better… I think it’s almost unarguable that it would be more efficient.</th>
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<td>If you’re talking about making products available for others to work with to test and evaluate to combine sort of the DNDI concept, TB Alliance, etc., then clearly there’s a giant leap in efficiency that’s potentially available because otherwise you’d have to wait until these products went off patent before you’d have any access to them at all.</td>
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<td>I think the other thing to keep in mind is the perspective from which you’re looking at this. If the objective of improved quality, improved efficiency is quicker, better advancement of products to the end user, to the sick patient or the subject in need then, I cannot conceive of a reason why this wouldn’t be beneficial from the end user point of view. From the standpoint of the developer, is this going to improve quality? Maybe. Efficiency? Maybe, but at what cost?</td>
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<td>So, I guess it could have one of two effects. Either it could be refreshingly revelatory and could encourage people to be hyper vigilant about the quality of the work that they do or it could have exactly the opposite effect and all of your work would essentially grind to a halt because you’d be afraid of exposing a vulnerability.</td>
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<tr>
<td>Efficiency might be slowed initially as something of this magnitude is implemented. Getting agreement by divergent stakeholders is TOUGH. Overall, and over time, the efficiency should improve. It will be very important to establish meaningful metrics that can be applied to truly determine the benefit over time.</td>
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<th>Participant Role</th>
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<td>CMO, CRO</td>
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<tr>
<td>CEO, Small Pharma</td>
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### Quote: Effects of OSRD on the Efficiency of R&D

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<thead>
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<th>Effect of OSRD on the Efficiency of R&amp;D</th>
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<td>Well, the old thing of data, information and facts… Before you have information you have a ton of data that you have to interpret somehow and it depends on who the “we” is. If you took it to its extreme then every single thing that the pharmaceutical company did would be public. And, that would be pretty much a disaster because people can’t interpret animal safety data for example. And there are multiple, hundreds thousands of cases that every single company has seen where you get some horrible toxicity in an animal and you find out that that particular species produces a metabolite that no other species including man produces and you’re only going to see that toxicity in that species and that’s in fact what happens, but you find that out later on. So, it depends on who has access to the data and who is doing the interpreting and there is so much “crack-pot” science out there and all you need to do is look at everything from rejuvenation to penis enlargement. So, there’s a lot of misinformation and a lot of misinterpretation of data that are there. So, in that context, that’s what I was talking about. There’d be too much data and it’d be overload essentially. But there’s a premise there I’m not saying I disagree with, but I’m not saying it’s true and that is the odds of success in pooling the data go up enough to cover the decrease in return and I actually don’t think that would happen. So you put five companies together, instead of getting one wise entity you simply have five entities coming together and still muddling through and so I think that’s the issue. I actually don’t think, because a lot of these things you can’t foresee, I just don’t think it’d work. It’s illogical to me to say we believe that the [OSRD] model is right for orphan or niche diseases, why wouldn’t it also be right for bigger diseases? There really isn’t that much in the way of true trade secrets. And to share just as we’re seeing with these orphan diseases, data that at the end of the day improves the outcome in terms of approval times, times to market and patient benefit, I find it illogical not to say that the same benefits shouldn’t be extended to broader populations.</td>
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<td>Quote: Effects of OSRD on the Efficiency of R&amp;D</td>
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<td>I certainly don’t see how [OSRD] could hurt, and I think that at least sometimes people would learn something that would improve their next shot. So, I can’t help but think that would happen. How often? That’s a little harder for me to say. We obviously think that all of our advice is very useful and very helpful…</td>
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<td>It’s definitely beneficial. There are currently a number of areas where investments by companies are duplicative even if they’re each aiming for somewhat different molecules and each really pursuing a strategy of not me too, but finding their own-targeted niche. Many of these drugs work on the same diseases or the same disease mechanism. In cancer, there’s more of a movement toward drugs that affect the same molecular pathway with some origin modifications that may be different tumor areas and maybe different subgroup of tumors, but again, they’re all relying on the same basic systems: biology and genomics. There are lots of areas where the time and cost of drug development is high because it takes a long time to figure out a reasonable degree of scientific certainty that a drug really does work or really does have safety side effects. It’s in everyone’s interests working in those same areas to have better ways of identifying problems and benefits in particular patients early, but again that’s something that’s very hard for individual companies to do on their own. So, there are a lot of applications. Like I said, caution on the other side that for some aspects that drugs really are just a molecule wrapped in intellectual property or knowledge and some of that knowledge results in clinical trials and the like. Probably will remain understandably proprietary, but that’s not to say there are a lot of areas where there is real promise in real open science approaches.</td>
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<td>If you move on to clinical development it really gets bad. The biomarkers, all those things for years they would come in to us and they would say, “Well you should accept this biomarker”. It’d be one company and as you well know the scientific process involves public scrutiny and evaluation by the scientific community and generally replication at different hands. And these companies all socialize the model of we’ll have everything in-house. They would bring us their own biomarkers and expect us to buy them. And of course, they would be mad at us because they’ve done a lot of work on this so the earliest effort with that was what the C-Path Institute did on the safety markers and they found that every large company had developed different safety biomarkers for animal studies and they had all kind of data on their performance because they did the study and they never shared any information.</td>
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References


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