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Transparency in the Time of Constant Change

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ABSTRACT

The time has come, after years of hard work, to submit your application to the regulatory agency for review and possible approval! What a relief to be able to finally hand off all of your hard work and, wait a minute, ensure that all data can be reproducible?!? While CDISC has been widely adopted and its SDTM and AdAM models widely implemented, there is still the need to understand the process of ensuring that all the data is a reflection of how it was originally collected, which in some cases can be very challenging. This paper will discuss some more trending ways of both creating and presenting data in ways that ensure it is consumable and can be understood not only for analysis/submission purposes but also that post-approval it is transparent and that everyone who has a vested stake can review the data in an appropriate way.

INTRODUCTION

With the publication of *Bad Pharma: How Medicine is Broken , and How We Can Fix it*, by Dr. Ben Goldacre in 2013 a bright spotlight was shone on the data behind/supporting clinical trials. A large part of his thesis is that pharmaceutical companies exaggerate the efficacy of successful trials and that, in addition to drug companies, regulators , physicians (who are educated by the drug companies) and even patient groups have failed to protect us. Another rather striking revelation was that a clinical trial with positive results is twice more likely to be published than one with negative results (although it should be noted that this specifically is related to results – the protocol is always provided). This selective publishing practice goes against the 8th revision of the Declaration of Helsinki, which states that “every clinical trial must be registered in a publicly accessible database before recruitment of the first subject”. Wow.

At about the same time Dr. Goldacre published his book, the European Medicines Agency (EMA) released for public consultation its draft policy on the publication and access to clinical-trial data. In its draft policy, the Agency defined three categories of clinical-trial data corresponding to different levels of access, as follows:

Category 1: ‘commercially confidential information’

This category covers clinical-trial data, information or documents that may contain commercially confidential information. These include, for example, the details of the investigational medicinal product itself, some in vitro studies or bio analytical data characterizing the product.

Category 2: ‘open access’

This category covers any clinical-trial data, information or documents that do not contain patients’ personal data. This information will be downloadable from the Agency’s website, at the time of publication of the European public assessment report (EPAR) for positive decisions, negative decisions or withdrawals.

Category 3: ‘controlled access’

This category covers clinical-trial data, information or documents containing patients’ personal data. These include individual patient data sets, individual patient line-listings, individual case report forms, and documentation explaining the structure and content of data sets. Protection of personal data is a fundamental right of European Union (EU) citizens, enshrined in EU legislation. For this category, two complementary levels of protection are foreseen to provide the best possible assurance against retroactive patient identification. Firstly, data will need to be adequately de-identified according to a recommended minimum standard. Secondly, access to these data will only be granted after the requester has fulfilled a number of requirements, including the signing of a data-sharing agreement.

Data transparency means a lot of different things and, depending on who is providing the definition, can have multiple answers. Is it to present pre-defined endpoints to a regulatory body, is to share actual data with regulatory agencies,

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competitors and/or the public at large? The answer is yes. For years Clinical Study Reports (CSRs) have been written which contain a plethora of information – literally every data collection point by individual and summary reports (although the summaries and patient level listings are often appendices or supplements to the CSR). Often these are thousands of pages long and it can be argued that the reader can lose themselves in the data, rather than find a specific answer. In addition to the CSRs, data have also been submitted to the US regulatory agency, the Food and Drug Agency, for years now. This enables the FDA to perform their own analysis, confirm the analysis carried out by the sponsor and ask intelligent questions about data that can be analyzed, confirmed and looked into prior to asking. It is highly likely that the Japanese regulatory agency, the Pharmaceuticals and Medical Devices Agency, Japan (PMDA) will be accepting data in SDTM format in 2016 as well (and requiring it by 2018), with the potential for the rest of world to be requiring it soon thereafter. This said, the amount of controversy and issues around disclosing (or not disclosing) comprehensive clinical trials results does not advocate specific programming techniques or try and determine what the 'correct' amount of disclosure is. On the extreme examples of this are those that advocate for transparency of data and results from the inception of a clinical trial, to those who are more cautious and would prefer to wait until the results are able to be repeated and demonstrate safety and efficacy over time to the hysterical public who believes that 'big pharma' is a single, monolithic entity designed for the sole purpose of taking as much patient, insurance and government money as possible. The discussion below will provide a more rational approach and explain some of the nuances about why none of these are entirely correct and/or possible. It will also provide clear examples about what industry is doing right now to address disclosure.

REAL LIFE EXAMPLES

To understand these nuances in more detail, particularly how it's possible for even patient advocacy groups to have failed us, let's look at the examples of Herceptin and Yervoy.

Herceptin: A whole book has been devoted to this exciting advancement in the treatment of breast cancer, titled *HER-2 : The Making of Herceptin, a Revolutionary Treatment for Breast Cancer*. This book does a terrific job in illustrating that even one of the most widely respected companies on earth, Genentech, who proudly touted they would "carry out research of the highest quality and then turn the results into new drugs with a swiftness that the staid pharmaceutical companies could not match." That was 1977, 19 years after the discovery of the HER2 gene and 21 even longer years before Herceptin's eventual approval. It also chronicles the trouble in being able to have results be reproduced as their [Genentech] colleagues failed to reproduce the results of their initial experiment. Also, as is the case with many drugs, Herceptin was misunderstood as a potential therapy to help any patient with late stage breast cancer and now it's recognized that it's arguably primarily a therapy to help patients with early stage HER2-positive patients as Herceptin blocks the overexpression of HER2 (which leads to progression of HER2-positive breast cancer).

Yervoy: After the results of a clinical trial with ipilimumab (Yervoy) were published a Forbes article summarized the results as follows: "Merck rival Bristol-Myers Squibb also unveiled promising melanoma drug results at ASCO from a study where patients were administered a combination of Yervoy, Bristol-Myers' existing melanoma drug, along with its developmental drug nivolumab. *This duo resulted in a 53% response rate* (the percentage of patients who saw a decrease in tumor size)." – italics mine. This drug is also very interesting – it has a novel mechanism of action in that it "It targets cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a protein found on the surface of T cells that acts like a brake; the drug removes this brake, allowing the T cell to go into attack mode and kill cancer cells." However, while this drug allows some patients to live up to 10 years (the longest follow up data as of this writing) the response rate is 10%-15% of all patients involved (depending on how you define patients – whether they were involved in the clinical trials or whether they were given it post-approval). However, as Dr. Goldacre may point out, a Google search of "What patients does Yervoy Help" results in the first six results being sponsored by its maker, Bristol Myers Squibb.

TRANSPARENCY IN THE TIME OF SOCIAL MEDIA

It seems paradoxical that we could know the very private lives of our favorite athletes, actors, and even authors (with the rare exception of JD Salinger) but not everything about the substances we put into our bodies. Years after the tobacco industry admitted its products contribute to the causation of cancer tobacco products are still being sold over the counter to anyone generally over 18 years of age. Needless to say, there is a large amount of momentum for the general public to not only see the analysis and interpretation of results from big pharma and regulatory agencies, but also to the public at large. With the plethora of internet search engines and social media sites it's almost unfathomable to understand how much data is out for consumption – and how inconsistent much of it is! From patient discussion forums (where there is so much needed hope for ongoing clinical trials – whether they have demonstrated efficacy in the standard double-blind placebo controlled randomized clinical trial) to the radical academics who paint a picture of a monolithic 'big pharma' conspiracy to the data actually presented by companies and sponsors in conjunction with regulatory agencies. On the more skeptical range of ideas, consider how much information the public has to the harms that smoking causes, and how many people still smoke. Is there reason to think that more information will lead to better decision-making by individuals? Is it reasonable to think that someone without the years and years of experience working on a trial can come up with a spurious result that demonstrates correlation but not causation? What would that mean and what impact may it have to a general public who is arguable used to reacting to sensationalistic news reporting?

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Let's try to answer that last question. There have been several examples discussed of why data transparency (e.g., would Herceptin have taken 19 years to bring to market, can the response rate of Yervoy be improved from 10%-15%?) is important and the advantages of having data disseminated to the public-at-large, but for purposes of simplicity we will focus on several of the most notable efforts, particularly some efforts that have arisen as a result of Dr. Goldacre's book - as well as some of the efforts of PhUSE itself. Having had the opportunity to work across several biotech/pharmaceutical companies over the course of the last 13 years, it's obvious that when there is a call to action (in this case to make results more transparent) a plethora of activities and initiatives arise that try to address the call to action. These can differ, even contradict it seems, to quite an extent between companies, and to a lesser extent, even within the same company. And in this case there are whole continents that are requesting access of data to all.

SPECIFIC CALLS FOR TRANSPARENCY/DISSEMINATION OF RESULTS

Outlined below are some of the transparency initiatives below, largely based in part on the examples provided in this paper:

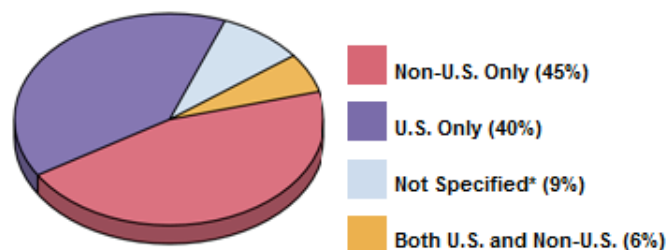
- +AllTrials (the result in large part of Dr. Goldacre's research, books and blog) – *Note: this does not call for individual patient data to be made publicly available*
 1. Registration
 - Self-explanatory
 2. Summary results reporting
 - summary of results should be publicly available where the trial was registered, within one year of completion of the trial. Summary results from all past trials of medicines currently in use should be made publicly available on a register now. Summary results include information on the primary and any secondary outcomes measured and statistical analysis
 3. A full report
 - In brief: Trial sponsors or others who produce a full report for marketing authorization or any other purpose should make this publicly available.
 4. Individual Patient Data – Note, again, that the AllTrials campaign is not calling for individual patient data to be made publicly available.
 - There are currently initiatives in many countries looking at how to improve sharing of this level of information for the benefit of future research. Patient groups, medical research funders and trialists have raised concerns about the inability to reuse past research. They are keen to develop consent protocols that will optimize the ability to reuse findings, and want legislators to look at whether new data protection regulations impose unnecessary burdens and restrictions on reuse of past research.
- PhUSE Working Group, Data De-identification: In the context of the EMA's policy on the publication and access to de-identified clinical-trial data, the PhUSE Board recently agreed to set up a Working Group that will drive an industry set of deidentified rules that are based on the CDISC SDTM data model. An announcement was made on 16th June and a large number of PhUSE members from Parma's, CROs, Software vendors and Academia have already volunteered to contribute to this initiative!
- SDTM/AdAM (CDISC)
 - No paper about data transparency would be complete without referencing what has made it possible to share data to the extent it's being shared now – CDISC. Simply put, CDISC open data standards have been developed collaboratively by global volunteers to improve the quality, efficiency and cost effectiveness of clinical research processes from protocol through analysis and reporting.
- Clinical Trials.gov (and EUDRA CT)
 - ClinicalTrials.gov is a registry and results database of publicly and privately supported clinical studies of human participants conducted around the world. This is one of the largest repositories of clinical trial information and will be talked about more in the presentation. This site provides a lot of summary information about which countries disseminate results, what types of trials are disclosed, etc. They also provide some very informative graphs, as demonstrated below, in Table 1:

Table 1 (<https://clinicaltrials.gov/ct2/resources/trends#MapOfStudies>)

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Percentage of Registered Studies by Location (as of September 18, 2014)

Total N = 175,013 studies



Location
Number of Registered Studies and Percentage of Total
(as of September 18, 2014)

CONCLUSION

With the publication of *Bad Pharma: How Medicine is Broken, and How We Can Fix it*, by Dr. Ben Goldacre in 2013 a bright spotlight was shone on the data behind/supporting clinical trials. While data has been provided to US regulatory agencies for years it's widely expected that Japan and other countries will follow suit soon. And with social media now being ubiquitous, there is a call by some that data can and should be provided to the general public. This paper also provided two specific examples of how transparency could perhaps have sped up the time from research to market as well as help find the right [sub] population for an oncology therapy. Lastly, some specific examples of how data transparency is being implemented were provided, as well as the number of trials (175,013 as of September 18, 2014!) were provided to clinicaltrials.gov. And it's worth stating again that no one is seriously advocating the disclosure of individual subject data, indeed it's arguable that the large part of the data transparency initiative is deidentifying individual patients – who did consent to the trial and are legally obligated to confidentiality.

REFERENCES

Bazell, Robert. *HER-2 : The Making of Herceptin, a Revolutionary Treatment for Breast Cancer*.
<http://www.fredhutch.org/en/news/center-news/2006/04/herceptin.html>
<http://www.alltrials.net/find-out-more/http://www.merriam-webster.com/dictionary/google>
www.yervoy.com
<http://www.cdisc.org/standards-and-implementations>
<https://clinicaltrials.gov/>
<http://www.businessdecision-lifesciences.com/>

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DISCLAIMER

The views expressed in this paper are solely those of the author.

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