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STATISTICS AND PROGRAMMING IN THE GLOBALLY EVOLVING LANDSCAPE OF CLINICAL TRIAL REGISTRATION AND RESULTS (CTRR) DISCLOSURE

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ABSTRACT

Following up on last year's topic, we discuss recent changes in the globally evolving landscape of Clinical Trial Registration and Results (CTRR) disclosure.

The presentation is informative for statisticians and management with beginner to advanced skill levels. CTRR disclosure is a cross-disciplinary topic relating to preparation and regulatory standards, management and career development, data analysis and visualization, and statistics including pharmacokinetics.

A recent survey of the DIA Clinical Trial Disclosure (CTD) community returned results that show CTRR disclosure is an activity that will continue to grow and require innovative programming shifts and changes throughout the next few years. Governing bodies are rolling out new rules and regulations while we try to comply with them, using new and ever-changing database environments.

In the United States, the US Department of Health and Human Services (DHHS) invited comments on their Notice of Proposed Rulemaking that outlined the changes they intend to include in the Final Rule before the end of 2015, which will affect how results are disclosed on ClinicalTrials.gov. [*Note: The anticipated date for the Final Rule recently was revised to February 2016 (or earlier, or later)].*

The EMA released Policy 70 that serves as a bridge between where we are today and where we will need to be to comply with the Clinical Trials Regulation in 2016. EudraCT will be changing dramatically because the new portal will not be ready to "go live" until sometime in 2017.

The China Food and Drug Administration (CFDA) is keeping up with change. The original Chinese Clinical Trial Register (ChiCTR) was retired in December 2014. The World Health Organization has accepted the new website as a clinical trial register. We will discuss some of their new processes and standards as well.

Discussion covers the most recent global changes, and their actual and anticipated effect on programming and statistical issues for preparing data tables for "anonymized" Clinical Study Reports, and for disclosure in regulatory databases that continue to lack a harmonized approach.

INTRODUCTION

This paper discusses recent and ongoing changes in the globally evolving landscape of Clinical Trial Registration and Results (CTRR) disclosure.

A recent survey of the DIA Clinical Trial Disclosure (CTD) community returned results showing CTRR disclosure is an activity that will continue to grow and require innovative programming shifts and changes throughout the next few years. Governing bodies are rolling out new guidelines and regulations while we try to comply with them, using new and ever-changing database environments.

The US Department of Health and Human Services (DHHS) invited comments on their Notice of Proposed Rulemaking that outlined the changes they intend to include in the Final Rule, and included a call for comments. DHHS intends to consider all comments received, so has postponed publication of the Final Rule again until February 2016 (or before). This Final Rule was called for in Section 801 of the Food and Drug Administration Amendments Act of 2007, and will clarify definitions and require process changes to comply with requirements to disclose clinical trial results on ClinicalTrials.gov.

The European Medicines Agency (EMA) released Policy 70 that serves as a "bridge" between where we are today and where we need to be to ensure compliance with their Clinical Trials Regulation published with an anticipated implementation date in 2016. EudraCT will be changing dramatically because it is a fledgling database for results, - and the new portal will not be ready to "go live" until sometime in 2017.

The CFDA is keeping up with change. The original Chinese Clinical Trial Register (ChiCTR) decommissioned in December 2014. The World Health Organization has accepted the new ChiCTR website as a clinical trial register. We will discuss some of their new processes and standards as well.

As the regulations and databases evolve, so do the ethical imperatives and guidelines. The EFPIA/PhRMA Joint Principles for Responsible Clinical Trial Data Sharing were finalized July 2013, effective January 1, 2014, and applicable to all member companies. Biopharmaceutical companies are committed to enhancing public health through responsible sharing of clinical trial data in a manner that is consistent with the following (3) Principles:

- Safeguarding the privacy of patients
- Respecting the integrity of national regulatory systems
- Maintaining incentives for investment in biomedical research

The announcement stated, "Biopharmaceutical companies will apply these Principles for Responsible Clinical Trial Data Sharing as a common baseline on a voluntary basis, and they encourage all medical researchers, including those in academia and in the government, to promote medical and scientific advancement by adopting and implementing the following commitments as of January 1, 2014:

1. Enhancing Data Sharing with Researchers
2. Enhancing Public Access to Clinical Study Information
3. Sharing Results with Patients Who Participate in Clinical Trials
4. Certifying Procedures for Sharing Clinical Trial Information
5. Reaffirming Commitments to Publish Clinical Trial Results"

The International Committee of Medical Journal Editors (ICMJE) updated their requirements for registering clinical trials in December 2014, and even the International Conference on Harmonisation (ICH) is changing their guideline for Good Clinical Practice. The ICH E6 (R2) Integrated Addendum: Good Clinical Practice reached Step 2 of the ICH process in June 2015. It is currently in Step 3, with Deadline for comments from MHLW by 30 September 2015, and from the US and EU by 31 Jan 2016.

To complement the harmonised ICH E6 Guideline, ICH integrates changes directly into several sections. This Addendum is proposed to modernize ICH E6 to enable innovative approaches to clinical trial design, management, oversight, conduct, documentation, and reporting that will better ensure human subject protection and data quality.

Once ICH E6 (R2) reaches Step 4 Sponsors must incorporate these changes in order to claim the trial was conducted under the standards of Good Clinical Practice (GCP).

Statistics and programming personnel will need to be intimately involved in implementing change to help sponsors gain and maintain compliance in this globally evolving landscape of clinical trial registration and results disclosure. It will require replacing departmental silos with cooperative interdepartmental strategic planning.

RESULTS FROM DIA-EFPIA WORKING GROUP

The DIA Clinical Trial Disclosure Community conducted a survey of sponsors during the period December 2014 – January 2015 to collect input in support of an EFPIA business case for harmonizing data elements across registries (particularly EudraCT and ClinicalTrials.gov). The number of responders to the 11 questions ranged from 14-26 depending upon the question, and respondents were from small companies (posting 1-5 records) to very large (posting 501-1000 records). Listed below are key messages from the survey results.

COMPANY PROCESS AND STANDARDS

- Only 4% of respondents expect to use one registry over the next two years, while 31% expect to use two registries and 31% expect to use six or more registries;
- The majority identified the following departments involved in their process: Centralized Clinical Trial Disclosures Group, Clinical Research/Study Manager, Biostatistics, Clinical Operations, Medical Writing, Regulatory Affairs, Legal – Patents, Local Country Affiliate;
- The highest percentage of companies (60%) have Internal Data Standards in-place; with slightly more than 50% indicating that a "global disclosure plan" was planned; and
- Given the options of reporting results manually, via XML upload or a hybrid of the two, the majority of responders indicated they report results manually on ClinicalTrials.gov (52%) and in EudraCT (57%).
- Of the 21 responders to this question, 43% do not have company websites.

NEED FOR HARMONIZED DATA ELEMENT DEFINITIONS

Of the responders, 26% are personally aware of issues of public misinterpretation because of incongruent information disclosed in the public domain.

- 71% identified the greatest benefit to harmonizing data elements across registries would be the ability to "Align Globally on Developing Internal Data Standards"
- More than 60% said that harmonization of the meaning of dates is essential to determining when registrations and results are due (e.g., start date, completion date, primary completion date, CSR date)

COSTS OF DISCREPANT DATA ELEMENT DEFINITIONS

There are significant differences in the time it takes to disclose results for a clinical trial (it depends upon treatment arms, periods, number of outcome measures, etc.), but some overall observations can be made:

- It takes much longer to post results on EudraCT than it does on ClinicalTrials.gov.
- If results were already posted on ClinicalTrials.gov, you would expect it to take far less time to post on EudraCT. However, because of inconsistent data elements and the resulting incompatible XMLs, that is not the case – it takes just as long for the second posting as it did for the original.

When asked to estimate the cost of providing results to multiple registries without having a global standard for reporting results, there were a range of answers, including:

- Frustration
- Monetary costs
- Compliance concerns
- Confusion

GREATEST BENEFIT OF HARMONIZATION IS DATA CONGRUENCE

When asked what benefit there would be if the data elements were harmonized, so the same information for the Clinical Trial Registration & Results (CTR&R) disclosure could be used in all registries, submissions and publications, answers included the following:

- Consistency
- Improved public perception
- Increased efficiency
- Reduced cost
- Improved compliance
- Cross-registry congruence
- Registry-publication congruence

US FOOD AND DRUG ADMINISTRATION AMENDMENTS ACT (FDAAA OF 2007), SECTION 801

There is to be a Final Rule in the United States (US) that describes the requirements and procedures for registering clinical trials and submitting their results, including adverse events on ClinicalTrials.gov, in accordance with FDAAA of 2007. Also proposed in the United States is a new Policy for NIH grantees, which will require all trials with NIH grant support to be registered and report results on the ClinicalTrials.gov, with no exceptions (such as for Phase 1).

NOTICE OF PROPOSED RULEMAKING (NPRM)

FDAAA called for the Final Rule to improve but not reduce the clinical trial information available in the ClinicalTrials.gov databank. To that end, on 19-Nov-2014, DHHS announced the NPRM, published it in the Federal Register on 21-Nov-2014, and opened a comment period to 19-Feb-2015 (which they extended to March to give sponsors more time to comment).

The NPRM proposes many changes, and requests comments and feedback on many more. After consideration of all the comments received, the current plan is to publish the Final Rule in February 2016 (or before – as early as this September).

The NPRM does not change the current requirements; it is a proposal issued for public comment in order for the DHHS to determine what future changes to requirements they will implement in a final rule. It also considers expanding the requirement for submission of results information for Applicable Clinical Trials to include drugs, biological products, or devices not approved, licensed, or cleared by FDA.

Of note is that the NPRM mentions NIH will expand its use of links between protocol records and additional explanatory material held by FDA, NIH, and/or systematic review information already publicly available. They will do random checks to see if data in the public domain (such as publications and submissions) are congruent with data in the protocol registration system (PRS - the database for posting information on ClinicalTrials.gov). The US FDA is granted authority by FDAAA of 2007 to fine sponsors up to $10,000 per day for each infraction until it is brought into compliance.

FINAL RULE (42 CFR 11)

As of 09-Jun-2015, the Final Rule is expected to be published in February 2016 (but it could be earlier or later).

Many of the required data elements are already in the Protocol Registration System (PRS), but will remain optional until the Final Rule. Sponsors need to get caught up and prepare so they're ready, because any new entries will have to comply with the Final Rule.

EFFECTIVE AND COMPLIANCE DATES

If the NPRM Subpart D is implemented, additional required information will be required in the data bank per 42 CFR 11:

- Effective Date **-** 45 days after the date final rule is published in Federal Register the PRS would be modified; the Responsible Party would have to submit information in a manner consistent with final rule
- Compliance Date - 90 days after the effective date of the final rule

COSTS OF NON-COMPLIANCE

With the Final Rule, compliance audits will likely begin. In the current disclosure environment, non-compliance would be a public relations nightmare in that non-compliance in one study record exposes all the sponsor's records to further scrutiny by the media.

Additionally, the US Food and Drug Administration (FDA) is charged with ensuring compliance. FDAAA of 2007 grants authority for the FDA to levy $10,000 per day per instance of non-compliance until brought into compliance. Since it takes between 30 and 45 days to get results prepared, reviewed, approved and released, this translates to potential fines of $450,000 per protocol.

EU POLICY 70 AND CLINICAL TRIALS REGULATION

The European Medicines Agency (EMA) assesses safety and efficacy of drugs in Europe and provides access to clinical trial reports on request as a part of EMA's access-to-documents policy from 2010. All clinical trials performed in the European Union are required to be conducted in accordance with the Clinical Trials Directive until the new Clinical Trials Regulation (CTR) EU No 536/2014 is implemented.

POLICY 70

Policy 70 is essentially a bridge between where we were in 2014 and where we need to be in order to comply with the CTR. In October 2014, the Agency adopted Policy 70 on publication and access to clinical trial data, wherein both on-screen availability (for any user) and downloadable clinical reports (for identified users) are outlined.

At this time, EMA is acknowledging that some redaction of existing CSRs is necessary before making them public, but there is a strong push to avoid putting any confidential information in the CSR going forward. TransCelerate is working on a guidance of best practices for writing "anonymized" CSRs.

This will affect the programming for data tables to be included in the CSR.

CLINICAL TRIALS REGULATION (CTR)

The CTR completely replaces the 2004 Clinical Trials Directive and impacts many areas, among them is clinical trial disclosure.

The CTR makes the Sponsor responsible to enter data into publically-accessible database via a new online portal – not EudraCT. It will hold data from trials conducted with at least one site in the European Economic Area (EEA) or part of a Pediatric Investigational Plan (PIP) including those "conducted outside the EU but referred to in a clinical trial application". In EudraCT, Sponsors with marketing authorization in EEA also must create their own EudraCT ID and post Third Country File results for non-EEA trials.

Clinical study reports will be required to be published within 30 days of market authorization or rejection and all information not agreed with EMA to be company confidential must be made public.

EMA provided required content for the Technical Summary of Results in Annex IV and content required for the Summary of Results for the Layperson in Annex V.

EU Clinical Trial Portal and Database

Article 80 and 81 of the CTR give the European Medicines Agency (EMA) the responsibility to establish an EU Portal and Database. The EU Portal will be a single entry point for submission of data and information relating to clinical trials required by the Regulation. The EU Database will contain all data and information submitted via the EU Portal.

The Portal and Database will facilitate:

- the application for clinical trials authorization, particularly multinational clinical trials, bythe sponsor
- the assessment carried out by the competent authorities of Member states
- access to clinical trials information by the general public

The new process for clinical trials in Europe will be contingent on the EU Portal and Database. Therefore, the implementation of the Clinical Trials Regulation is dependent on their full functionality, which will be confirmed by independent audit.

EMA had a public consultation on draft specifications for the EU portal and EU database to be audited, that closed on 31 October 2014, which was endorsed by the EMA Management Board on 14 December.

EMA is working with the Member states and the Commission to set up the portal and database, but in May, they announced that the portal will not be functional before 2017. This means the transition from EudraCT will be delayed.

The EU Clinical Trials Regulation is to be effective when the portal is ready, and no earlier than 28 May 2016. It is expected the portal will not be ready until well into 2017, so we will continue using EudraCT for some time.

CFDA AND CHINESE CLINICAL TRIAL REGISTER (CHICTR)

CHINESE FOOD AND DRUG ADMINISTRATION (CFDA)

The CFDA is keeping up with change. The timeline below reflects recent activities.

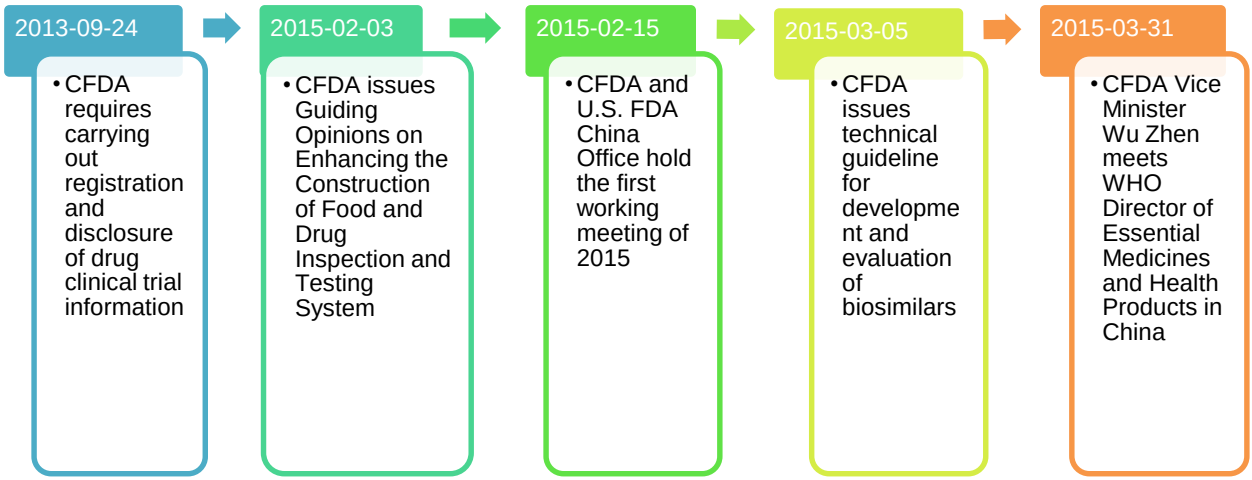

Figure 1. Timeline of Recent CFDA Activities

CHINESE CLINICAL TRIAL REGISTER (CHICTR)

On December 1, 2014, the original ChiCTR website (http://www.chictr.org/en/registry.aspx) was retired. No longer can sponsors use it to register studies.

The number of clinical study registrations has increased, and China updates the records on the WHO International Clinical Trials Register Platform (ICTRP) weekly now, instead of monthly. The old database could not work well enough for this new demand.

The updated database of the same name (ChiCTR- available at www.chictr.org.cn) is hosted by the Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University and provides services including:

- register for trials
- consultation for trial design
- central randomization for an allocation sequence
- peer review for draft articles and training for peer reviewers

It is a non-profit organization established according to both the WHO ICTRP Standard and Ottawa Group Standard, so registering a clinical trial is free (no charge). There is a charge only for those needing help to improve their study design. ChiCTR provides services including trial registry, consultation for trial design, central randomization for an allocation sequence, peer review for draft articles, and training for peer reviewers.

ChiCTR has described the trials that should be registered as:

“All studies that aim to evaluate the effects on human subjects by interventions including drugs, non-drug treatment, instruments and equipment designed as a randomized controlled trial or case-control study, or cohort study, or non-controlled study or other any observational studies of prevention and treatment, prognosis studies, cause studies and diagnostic tests should be registered.”

INSTRUCTIONS FOR REGISTERING A TRIAL ON CHICTR

There are instructions for registering a trial on the website as follows:

- At first, you should establish your personal account in ChiCTR website then, login and select "Project info", "Project management" at left side, and then select "New" at the top of the window. You can start application for registration by filling in the electronic registration form online.
- ChiCTR will review the suggested project according to the registration criteria;
- If there is anything unclear, they will contact the registrant to discuss or require they provide necessary data by phone or email;
- If the trial is considered eligible for registration, a registration number will be released.

- A universal trial number (UTN) may be requested from WHO ICTRP within four weeks after registration (at http://apps.who.int/trialsearch/utn.aspx) which is entered as the "Secondary ID" on the ChiCTR registration form.

There are two very important requirements:

- The registrant has to provide a copy of ethics approval letter and the study protocol including informed consent which should be uploaded via registration form. The protocol will be used only to help ChiCTR to understand the study design when they perform the review, and it will not be published.
- For the purpose of promoting the quality of clinical studies, the protocol has to be developed according to the GCP standards. If not, the application for registration will be rejected.

The Declaration of Helsinki (2008) requires that any clinical study involving humans should be registered on a public clinical register before recruitment of the first participant.

Originally, ChiCTR stated in 2007 that they will accept the retrospective registration until January 1, 2008; in 2011, then they extended the deadline for retrospective registration to January 1, 2013.

Because there remained many researchers applying to register their studies retrospectively, ChiCTR decided that anyone hoping to register their studies retrospectively must provide the raw data of the study to be evidence that the study existed, and the raw data should be publicly accessible.

The raw data must be provided via ResMan, the public management platform of clinical trials database. The use of ResMan is voluntary, for public welfare. One can apply for free use without charge. Payment will be required just for those who have research funding. Anyone not approved to waive the charge of the database should pay no more than 3,000 yuan RMB (500 USD) for the database occupation and service of reviewing the raw data."

ISSUES AND STATISTICAL CONSIDERATIONS IN THE EXISTING PRS AND EUDRACT DATABASES

As disclosure requirements evolve, substantial changes are being made to both PRS (Protocol Registration System – US) and EudraCT (EU) registries. Some of those changes require re-programming of SAS data sets to obtain the required information in ways the systems will accept.

PROTOCOL REGISTRATION SYSTEM (PRS) FOR DISCLOSURE ON CLINICALTRIALS.GOV

The PRS separates results into the following modules:

- Participant Flow
- Baseline Characteristics
- Outcome Measures and Statistical Analyses
- Adverse Events

XML FILE TRANSFER

The PRS provides XML file transfer (upload) capability to facilitate the transfer of data into ClinicalTrials.gov from the data provider's computer systems.

XML files, which may contain either protocol or results information, or both, to be uploaded into the PRS are subject to the same validation process as protocol/results records created manually within the PRS web interface.

It is possible to upload either the Protocol or Results XML, or both. The Protocol and Results XML Schemas available in the PRS define the specific required and optional tags associated with the Protocol or Results section of the clinical trial record.

The data provider can download one or more records, including results, into an XML file on their own computer, and account administrators can download XML for all the organization's record into a single XML file.

Uploaded records are not released for publication on the ClinicalTrials.gov website automatically. Records uploaded by an Administrator that pass validation without any errors receive a record status of "Approved", while records with errors receive "Entry Completed" record status. Sponsors may correct errors by repeating the upload, or manually, using the PRS web interface. When using the web interface, they must approve the record manually as well, because approval is required for records released to ClinicalTrials.gov.

Records uploaded by a regular User have a record status of "In Progress" and thus must be Entry Completed, Approved and Released in order to be published on ClinicalTrials.gov.

Note that an uploaded record replaces the previous version of the record if one exists. However, the previously Released version will continue to be made public on the ClinicalTrials.gov website until the new version has been Released and has passed PRS Review by ClinicalTrials.gov. All released versions are maintained in an audit trail that is accessible to the public.

EUDRACT FOR DISCLOSURE ON THE EU CTR WEBSITE

Sponsors are responsible to post results as a pdf attachment only or as a full data set (with or without a pdf attachment). The sponsor may post just a results summary only for trials that do not include a paediatric population and ended on or before 21 July 2013. The sponsor must provide a full data set for all other trials (including phase I) that have a EudraCT number and ended after 21 July 2013, as well as any that included a paediatric population, even if posting retrospective results.

If a sponsor is market authorisation holder in the European Economic Area (EEA) for the product under study, but there were no sites in the EEA, the sponsor must create a EudraCT number and post a Third Country File (similar to a trial registration). Only then can they post the required results.

The EudraCT system indicates record status in one of three ways within the system:

- Draft, meaning the user is preparing the results in the system.
- Posted, meaning the user has satisfactorily validated the results and released the record for publication
- Finalised, meaning a 14-day waiting period has elapsed, the results are final and can be viewed on the EU CTR (if the protocol related records have been published)

There are data elements, particularly concerning Adverse Events that are not required in the PRS, and since the XMLs are not harmonized, programmers need to know that it is essential to use the correct XML schema for each registry – they are not interchangeable.

CONCLUSION

CTRR disclosure is an activity that will continue to grow and require innovative programming shifts and changes throughout the next few years. Governing bodies are rolling out new rules and regulations while we try to comply with them, using new and ever-changing database environments.

Clinical Trial Registry and Results (CTRR) disclosure and journal publications too often are considered the final (and separate) steps in the clinical trial process. It is actually necessary to collect data elements throughout the clinical trial lifecycle, from many functions along the way. Only by breaking down departmental silos and creating cohesive interdisciplinary teams is cross-venue data congruence even possible.

Multiple industries have used the principles of Quality by Design (QbD) –building quality (and compliance) into process – to advance product development. As recently as 2008, the US FDA adopted QbD to transform drug discovery, development, and manufacturing.

At Xogene Services we apply QbD to clinical trial disclosure by using a process through which all relevant data elements are collected in a single living document, reflective of the entire trial lifecycle from study start-up to results. Using Quality by Design allows the reprogramming to take place ahead of time rather than as an afterthought. It allows identification of disclosure data elements before the protocol is even written - thereby streamlining work, saving time, effort and cost, while supporting regulatory compliance and audit preparedness.

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