Autumn 2015 • ISSUE 92

acdm
association for clinical data management

DataMatters

www.acdm.org.uk

ARTICLES

ACDM NEWS

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NEWSLETTER DEADLINES AND PUBLICATION DATES

If you would like to submit an article to the Newsletter or include an advertisement, then the following dates will help you plan:

Issue	Copy Deadline	Publication
Winter 2015/2016	04 January 2016	1 February 2016
Spring 2016	18 March 2016	3 May 2016
Summer 2016	17 June 2016	1 August 2016
Autumn 2016	16 September 2016	7 November 2016

ACDM eShots

ACDM notices can be included in our twice monthly eShots sent around the 1st and 15th of each month. ACDM advertisements should be emailed to the ACDM office 6 working days in advance.

ACDM ADVERTISING

You can now advertise with the ACDM in the following ways:

- eShots are informative email communications sent to all registered members and non-members, highlighting relevent news and events from the ACDM and across the industry. Your advertisement will be included at least twice a month.
- *Data Matters* features articles on industry news and issues and ensures your advertisement will be viewed by an active audience of more than 1,200 data management professionals.
- Web Site *www.acdm.org.uk* now provides prime banner advertising space as well as the classifieds section where your advertisements cannot fail to be noticed.

Not only will your advertisement reach all ACDM members but also the wider community of data management and other professionals who access the website directly or click through from our eShot.

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Effective from 1st February 2010

Newsletter

Full Page Colour* £300
Half Page Colour* £200

Web Advertising (under recruitment or services)

One month* £150
Renewal per month (no changes) £100
Annual advert (up to 6 updates) £700

Website Banner advert – Home page

One month £200
Renewal per month (no changes) £100
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Website Banner advert – other pages (excluding home page)

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One month (eShot sent at least twice a month) £150

* bulk discounts available – please contact the ACDM office for details (Tel: +44 (0) 1727 896080, email: admin@acdm.org.uk)

Download the latest advert specification sheet from the adverts section of www.acdm.org.uk

All items, excluding membership and publications, will be subject to VAT

Guidelines for Contributors

Articles range from 700 words to over 2,000. Photographs, diagrams and illustrations help to break up large areas of text. News items can range from 80 – 400 words to include photographs if relevant. Profiles can range from 300-600 words, and photographs will enhance these pages.

Photographs – We need good quality digital images taken at the highest resolution possible. With digital photography the more mega pixels the camera has, the better.

Illustrations – Charts and diagrams drawn in Excel or Word will normally need to be redrawn for the printing process. If images are embedded in Word documents they need to be supplied as separate jpegs as well.

Preferably, articles should be sent via Email or CD. Plain ASCII text is best, but many WP formats can be imported. Contact the Editor for help if you are unsure.

All articles should be sent to the Editor in good time for the copy deadline. Articles may need to be edited to fit the constraints of publishing, with full text available on request. All articles are subject to editorial approval.

The opinions expressed within this newsletter are those of the individuals concerned and not necessarily those of their employers or of ACDM. All advertisements included with it are done so independently and the Editor reserves the right to refuse any, which, in his opinion, do not conform with ethical advertising standards.

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NEWS

ARTICLES

Members are the life blood of our Association

Over the last year, there have been many positive steps forward in the association. However, we continue to have many challenges. Our financial situation is moving in the right direction by prudent budgeting and management of our costs. This has allowed us to continue to develop some of our key membership offerings. An excellent example of this is our training offering, which has been given a complete revamp, and, for the first time, we can deliver independently accredited training courses that can support your continuous professional development. We have just awarded accreditation certificates to our first data management professionals and the breadth and depth of work to achieve this recognition is extensive. Further information will be circulated on the courses and benefits in the very near future. We believe we have the industry leading training offering and need your support to increase the visibility of the ACDM's training offering within your company.

The eClinical Committee continues to expand and develop with the leadership of Rob Nichols. This committee is made up of senior level representative from pharma, CRO and technology companies and it is thought leadership sessions will drive much of the content for our newsletters and trainings of the future.

Since their introduction, Hot Topics have been well attended and we continue to invite suggestions for topics. We would welcome all members to contact us if they have any topics they feel would benefit our membership.

Membership renewal is upon us and one of the Board's main goals is to increase membership numbers. We appreciate times are difficult; companies are questioning every penny and also not allowing people to travel to events like the ACDM. However, you are the life blood of the Association and we do appreciate all of your support and engagement.

ACDM are always looking to work with other like-minded associations to serve our CDM community and, if you are a member of an association with similar goals, we would love to hear from you.

We continue to invest and be prudent with our costs so we will be able to continue supporting the every changing CDM professional landscape. However, to do this, we need more committee members and board members to bring new ideas and support to the association.

Kind Regards

Emmet Browne and Jon Wood, Co-Chairs ACDM

Newsletter
Committee

Newsletter Committee Report


Jean Cornhill

Newsletter & Newsletter Committee

Firstly, apologies for the lateness of this Newsletter. Since the beginning of the year, apart from myself, there have been no other Committee Members on the Committee as the other people are no longer on the Committee.

Unfortunately, I have to also inform everyone that the J C Amos Article of the Year Award has been stopped. Thanks to everyone in past issues who submitted articles to be judged for the award and to some who actually won the award.

Secondly – great news. Ali Roskell (nee Green) is rejoining the Newsletter Committee after a few years' break.

I am still on the lookout for additional committee members so please contact me if you are interested in joining the Committee by sending an email to editor@acdm.org.uk

Committees & Special Interest Groups (SIGs)

Committees and SIGs are desperate for new members – why not take a look at the back page of the newsletter or log on to the ACDM website to see if there is anything of interest to you.

Member Feedback and Comments

It would be useful to receive feedback and comments from readers to be shared with those reading Data Matters. If you have anything to say or questions to ask authors or members, please send by email to editor@acdm.org.uk It would be interesting to receive some feedback to share with everyone.

Thank you for your time and I hope that you enjoy reading the rest of the Newsletter.

JEAN CORNHILL - Chair/Editor – Newsletter Committee

Newsletter Articles

I know that I have said this before, but in order to make this a Newsletter for all members, we do need input from you to provide articles. Just because there is no longer a money incentive to provide articles, this is your Newsletter so please try to write even a small article or comment or submit questions on a previous article.

Some time ago, we announced that we had hoped to publish articles on all stages of clinical trials to improve understanding and awareness of responsibilities of other areas in the clinical research journey. If you would like to offer or know of anyone willing to write an article on any stage (e.g. Project Management, Regulatory, Clinical Monitoring, Data Management, Statistics/Programming, Medical Writing, Safety, Quality Assurance, Quality Management, Post Marketing), please let me know. As always, we would like to include articles from both a Pharma and CRO perspective. Articles may not be needed immediately or they could be written now and held by us for a later publication.

Remember that you do not need to wait to be approached before you write an article – you may submit an article at any time to the editor's email address (editor@acdm.org.uk).

As mentioned before, articles can be on almost any subject – either industry related or something more personal. This could be a 'Day in the Life of ....' so that you can explain a typical, or perhaps not so typical, day in your job role. You may like to make everybody jealous and report on a wonderful holiday destination. It may be on a life-changing experience which you are happy to share with members.

WRITTEN BY STRATEGIC AND OPERATIONAL EXPERTS FROM THE PHARMACEUTICAL INDUSTRY AND ACADEMIA

Learn How To Successfully Deploy e-Clinical Systems For Use in Clinical Trials in a Regulated Environment

The CR-CSV Working Party is pleased to announce the publication of "Validation and Management of e-clinical Systems in Collaborative Clinical Trials"

The CR-CSV Working Party is an industry group that has been supporting the clinical research community for 20 years, providing guidance and education on the subject of computerised system validation in clinical trials.

Following the release of the 1st and 2nd editions of the ACDM/PSI "Computer Systems Validation in Clinical Research" guideline it was recognised that there was a growing need in this area for guidance on collaborations between industry partners (such as pharmaceutical companies) and research organisations (such as Academic Research Organisation, Universities and NHS).

These types of collaboration present significant challenges in terms of managing expectations and achieving acceptable levels of compliance to regulatory requirements governing the use of e-clinical systems in clinical trials.

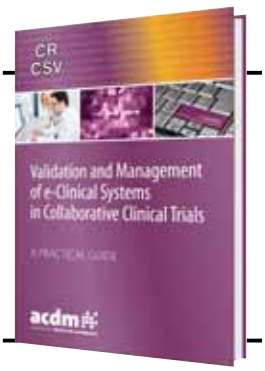
The new guideline uses an approach based on worked examples to illustrate the steps needed to ensure that any e-clinical system is trial compliant and inspection ready.

ORDER YOUR COPY TODAY!

Copies of the guideline are available via the ACDM website

www.acdm.org.uk/resources.aspx

***These will be available from 10 December 2015.**



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For further information please contact collaborationguide@gmail.com

acdm conference
NETWORKING | EDUCATION | SUPPORT 2015

ACDM Annual Conference

Husa President Park, Brussels • Wednesday 18th March 2015

This year's conference saw a departure from our usual format of a two day conference in the UK, to try something a little different, a one day European conference packed with as much content as we could squeeze in and positioned to support our European members as well as allow those of us from the UK to attend.

The result was a fabulous conference in Brussels, just a short train ride away for most of our members, both European and British, the attendance at the conferences was great, supporting the decision to vary the conference presentation, and the support from sponsors and exhibitors exceeded our expectations, so I would like to extend the ACDM's thanks to all who attended, as delegate, sponsor, exhibitor, presenter or organiser. It would not have been so successful without your support.

Presentations

Dr Kevin Fong opened the conference with a 'big bang' this year, with his look at the medical revolution in health-related apps and gadgets based on his Horizon documentary 'Monitor Me'. We learned about the England Rugby 7s team, whose coach knows more about his players' health than a doctor would, to the most monitored man in the world who diagnosed a life threatening disease from his own data, without going to the doctor.

Jonathan Andrus of BioClinica, who kindly sponsored Dr Fong's attendance at the conference, followed this presentation with a look at how participants can use tools and technologies available today to create risk-based data management monitoring plans for the effective management of their clinical trial data by looking at real-world examples.

After coffee, **Claudio Garutti, Oracle**, discussed the data best practices and critical capabilities around clinical biomarkers and how sponsors can deal with them to leverage biomarkers in clinical research. While John Kline followed with a detailed look at how the growth of mobile platforms has enabled the development of wearable devices and their combined impact on transforming clinical trials.

> "The result was a fabulous conference in Brussels, just a short train ride away for most of our members, both European and British.

Maibritt Haugaard Møller, Larix A/S gave us some insights into risk-based approaches to system validation through case studies and a high level look at the latest validation project implemented at Larix. Followed by **Tomás O'Mahoney, (EUCROF, European Union CRO Federation, Late Phase working Group)** who looked at non interventional studies and how following inappropriate processes can have a negative impact on the study progress, as well as giving us some guidance as to how this situation can be avoided.

Just prior to the lunch break we had a great panel discussion with **Dr Kevin Fong, Demetris Zambas** and **Lorenzo DiCarlo** where we all discussed the different healthcare apps on the open market and how these could fit into the clinical trials arena, we had some great input from the delegates as well as the panel and all agreed there was a lot of potential to be tapped into as long as the technology can work within the regulations.

A slight change to the published agenda took place as **Lorenzo DiCarlo**

Focus on Sponsors and Exhibitors

We would like to thanks the following Sponsors and Exhibitors for their support.

from Proteus Digital Health took to the stage immediately after a particularly good lunch and talked to us about their CE- marked ingestion sensor which has been developed that is the size of a poppy seed to be used to monitor medication adherence.

Jim Streeter, from Oracle looked at how this technology can be used in a clinical trial setting to ensure medication adherence, helping to determine the optimum range between the dose-response curves for both desirable drug effect and unwanted drug toxicity, and ensuring greater compliance with the trial protocol.

This was followed by the ACDM annual general meeting and a further coffee break leading us into the final session of the day. **Demetris Zambas from Norvatis** took the stage and discussed the transformation that eSource is bringing to the clinical setting of a trial. In particular looking at the data management aspects of implementing eSource and the need to not simply replace paper with eSource, but to manage changes to the whole process before true transformation can occur.

And we closed with **Richard Perkins** leading us through two presentations, firstly an update from discussions with the FDA regarding eSource on the Contemporaneous Independent Investigator Copy/A proposal for defining procedural, contractual and contractual conformance, secondly, on the preparations for deployment of EHR4CR.

Survey results

As usual we asked for feedback on the conference, this time using an online survey sent at the end of the day rather than the previous handheld devices at the conference. It highlighted the importance of the ACDM eShots and word of mouth in your attendance at the conference. As well as the importance of not only the program content, but also the networking in your decisions to attend. Luckily we scored highly on your rating of the program content, so I hope that you were all pleased with your decision to attend. The exhibition was enjoyed by most and was a fitting complement to a one day event.

> “The attendance at the conferences was great, supporting the decision to vary the conference presentation, and the support from sponsors and exhibitors exceeded our expectations.

We had good feedback on the conference brochure, and joining documents, but had some issues highlighted to us with regards to the online registration and conference website which we will endeavour to improve next year.

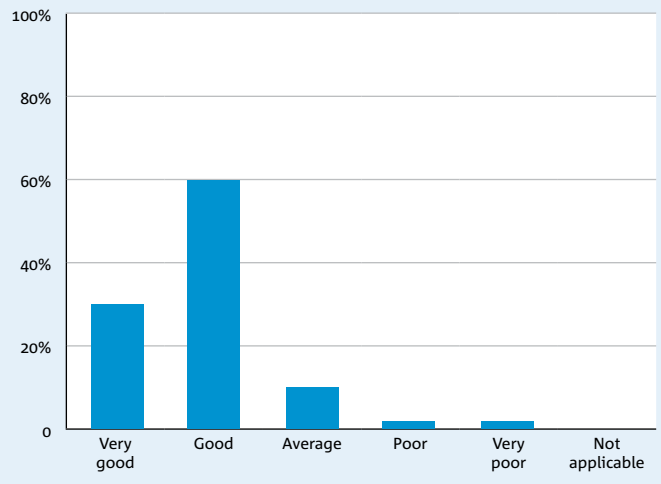
The venue proved popular, with very few negative scores or comments, and the location and access to it scored even higher. Confirming that our decision for a European conference had been a success.

The accommodation also scored well and it seems that the refreshments and lunch were particularly enjoyed by everyone.

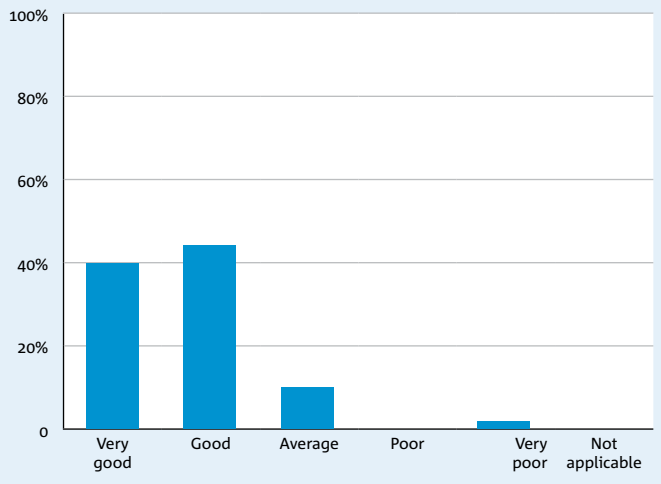
In conclusion I would like to re-iterate the ACDM’s thanks to all who attended, as delegate, sponsor, exhibitor, presenter or organiser. It was a highly successful one day event which was thanks to your support.

Next year we will repeat the one day format in London, dates and venue to be released soon.

Q9 The conference venue



Q10 Location and access to the conference venue



Hot Topic Discussion: MSSO introduce a 27th SOC in the MedDRA Dictionary

As of March 2016, MedDRA version 19.0 there will be 27 System Organ Classes in the dictionary.

The 27th SOC as yet unnamed is being developed in order to capture Product quality issues that are abnormalities that may be introduced during the manufacturing/ labelling, packaging, shipping, handling or storage of the products.

On the 10th of December this was the subject of an ACDM Hot Topic Discussion Webinar with a presentation by Patrick Revelle Director of the MSSO and Judy Harrison Chief Medical Officer MSSO. The discussion was hosted by the ACDM Coding SIG Chairs Jo Staniforth (Roche) and Barry Hammond (Data Standards & Medical Coding Consultant, Terminologeze) .

The presentation explored the reasons and rationale for a 27th SOC. (The slides are available to view on the ACDM website). Judy Harrison (MSSO) spoke about the current scope of MedDRA, and how it was on the recommendation of Blue Ribbon Panel held in April that the decision to create a 27th SOC was reached.

At the moment the structure and the contents of the new SOC is under discussion and public consultation is taking place during 2015. The MSSO are looking to collaborate with MedDRA and Quality experts and are keen for input on their proposals. Anyone interested in participating can send an e-mail to the MSSO help desk.

During the webinar there was then a Q& A session much of which was concerned on how we disseminate this information to other areas that will be affected by this change that may not be directly involved with the MSSO such as Stats and Programmers.

The other main question was concerning the impact on IT systems.

These concerns are being addressed by the MSSO by providing at least one year of notification, aiming to deliver the message in as many forums as possible, through the creation of a Developer focused webinar and a document describing the technical change.

The Scope and use of new SOC will be available from MedDRA.org and MSSO Help Desk along with Webinars, User Group meetings, training sessions and videocasts.

If you have any questions about this change or any aspect of coding please contact the Coding and Dictionaries SIG.

Jean Hogan
Clinical Coding Specialist Biometrics
Roche

Non Intervention (NI) Studies

7 simple rules to better data management and 4+1 for improved Pharmacovigilance in NI Studies

Introduction

Non-interventional studies (NIS) are an essential part of the clinical development program. The term non-interventional studies includes post-marketing surveillance studies (PMS), as well as disease or drug registries, observational studies and post authorization safety studies (PASS) that can be imposed by competent authorities. Over 18% of the clinical studies registered on clinicaltrials.gov site are observational studies (or 35,146 data as of March 10, 2015)[1]. While in clinical trials the efficacy of an investigational product is explored in a patient population which has been selected according to strict inclusion and exclusion criteria, in non-interventional studies patients are treated under real life conditions. The fundamental difference between a clinical trial and a NIS is that the data collection or patient-participation in the NIS does not interfere with the choice of treatment, sample collection, procedures, or the treatment itself, all of which follow standard practice of care. The patients in this type of study will receive the same treatment and diagnostic procedures as they would have received if they were not included in the study.

Similar project tasks are performed in clinical trials and NI studies (e.g. protocol writing, Ethic Committee (EC) applications, eCase Report Form (eCRF) specification and data management) and this often leads pharmaceutical companies and Contract Research Organisations (CROs) to believe that they can follow the same processes and standard operating procedures (SOPs). What is unique to NIS is perhaps the study size, we see patient numbers increasing to thousands and shorter observation periods than in Randomised Clinical Trials (RCTs). A recent national study we performed involved 7000 patients across 700 sites in the Russian Federation. The approach outlined in this paper was used in the eCRF specification and data management for this study.

In this environment, however, and in particular with the number of NIS on the rise, there is a need to seek efficiencies in the processes and procedures. This begs the question; is the blanket application of procedures developed for earlier phase studies creating inefficiencies in NIS? At the European CRO Federation (EUCROF), we know, from shared experience, that running NI studies along the same processes can lead to inefficiencies and added cost for both the clinical investigator teams and our staff. In this article we are going to highlight how following inappropriate processes can have a negative impact on the study progress. We will also provide some guidance as to how this situation could be avoided.

Demand for late phase trial services will drive growth to 2023 according to a recent marketing report [2]. For quite some time now there has been an opinion that NIS evidence is complementary to randomised clinical trials[3] and data are usually published and made available for the scientific community; meaning that results have to be robust and reliable. It is essential that clinical teams are less burdened and that data cleaning can efficiently deliver a clean data set suitable for analysis and reporting of study outcomes.

> “What is unique to NIS is perhaps the study size, we see patient numbers increasing to thousands and shorter observation periods than in RCTs.

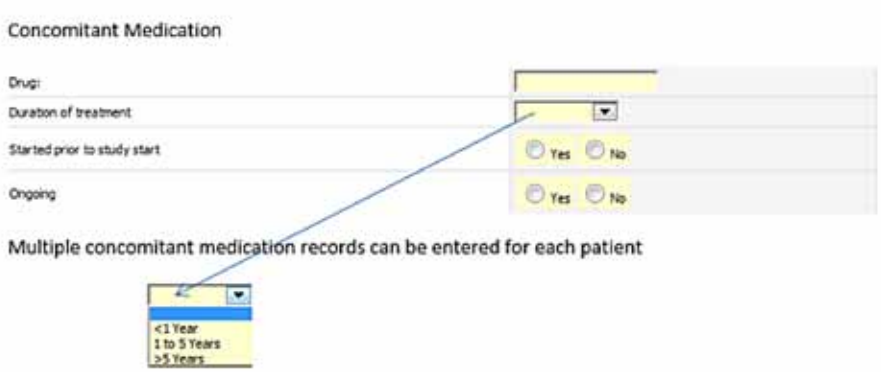
Rule 1: Understand and identify the important data.

The primary outcome data and safety data is important and therefore the data validation focus must be here. After that we need to stop and think; which data addresses the objectives?

In an observational setting, it is quite common for sponsors to add several secondary objectives to make the most of the large population examined and the period of observation. It can happen that, from the sponsor’s point of view, some of these secondary objectives could have the same strategic importance of the primary objective. Often the relative importance of the secondary objective vs the primary one can be ambiguous due of the specific needs of the sponsor. As a result, data related to secondary objectives should be managed based on the needs of the sponsor.

We must, however, ask ourselves whether we need to run all the standard checks that we use in other studies i.e. start date before stop date, visit sequence dates, height checks, and weight checks. This uncertainty is compounded by the fact that CRF and database design in NIS has largely incorporated standard forms taken from clinical trials CRFs e.g. concomitant medication pages, Serious Adverse Event (SAE) pages, vital sign pages and laboratory pages. These standard forms may not be appropriate to the more important study outcomes in NIS, but when utilised data management feel

Figure 1: Late Phase concomitant medications page template



obliged to run all the usual checks.

We are caught between a rock and a hard place. How can we change this? Let's come back to that one.

I hear it said, that if we don't analyse the data we should not collect it. However, at the design stage it is often very difficult for a sponsor representative to answer the question: "Do we really need this data?". Therefore, rule 2 may assist.

Rule 2: Only collect the necessary detail

The protocol writer does not always review the work of the CRF designers and when we use Sponsor Standard Forms, e.g. concomitant medication forms or SAE forms, it is common that additional data i.e. stop start dates from concomitant medications that are not used in the analysis, are collected. These forms are standard for early phase work but when we conduct post approval work we should really develop new standard templates.

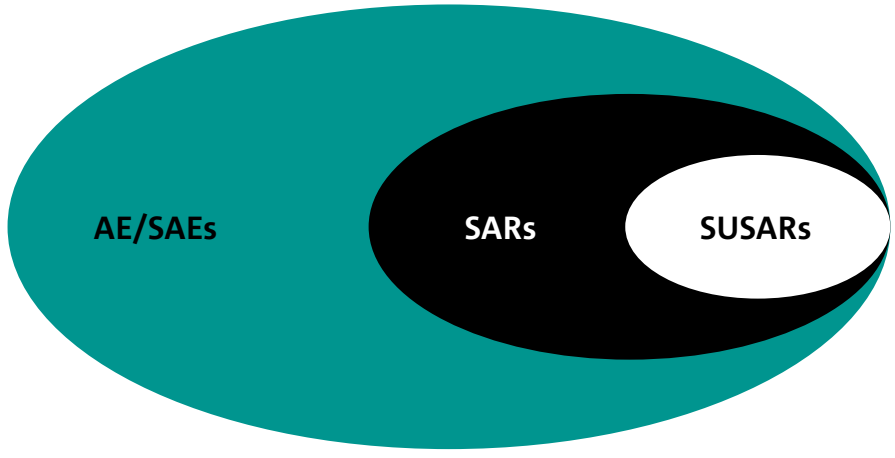
In NIS it may be that concomitant medications information is collected to support Adverse Drug Reactions (ADRs) cases. Therefore we do not require the same level of detail as in Randomised Clinical Trials (RCTs). It is probably sufficient to have the medication, the dose and an estimate of how long the patient has been receiving this medication e.g. less than 1 year, 1-5 years or greater than 5 years. A simple design change like this can significantly reduce the data management and clinical staff workload. See Figure 1 for a late phase concomitant medications data template.

Similarly, the standard AE/SAE forms for clinical trials are very often stand-alone case studies which are processed by the Pharmacovigilance department and used to build up the product safety profile. This results in a good picture of the safety profile of the product by the time of product launch. Of course we can learn more from the non-controlled sample population that participate in non-intervention studies and we know that under-reporting of ADR is well documented in the literature[4].

The important thing should be that all suspected ADRs are reported and the initial detail should be secondary. We would recommend that the big four are recorded i.e. the product, the event, the patient identifier and the credible reporter; + 1 is the causality i.e. is it related to the product? If we capture minimal data we are encouraging the reporting of events by making the process simpler - ask for less and you will get more. We will have the initial report with essential information - this is a good thing. By simplifying the reporting we may get a better safety profile of the drug in real world practice. Marketing authorisation holders must have mechanisms in place to collect full and comprehensive cases information at the time of initial reporting, in order to allow meaningful assessment of individual cases and expedited reporting of valid Individual Case Safety Reports to competent authorities as applicable. The point here is that the eCRF should only contain the initial minimum information and this can be followed up through Pharmacovigilance processes for support data that is not included in the CRF. Uncoupling the study database from the PV database is not intuitive but it will be more efficient.

In accordance with the current legislation[5], only serious ADRs are required by the competent authorities in NI studies (see Figure 2). All serious ADRs should be reported within 15 days of becoming aware of the adverse reaction. The periodic safety update report (PSUR) is intended to provide an evaluation of the risk-benefit balance of a medicinal product and will be

Figure 2: Serious Adverse Drug reactions are more relevant to NIS.



submitted by marketing authorisation holders at defined time points during the post-authorisation phase. However PSUR may not be required for low-risk or old products (generic medicinal products (DIR Art 10(1)), well-established use medicinal products (DIR Art 10a), homeopathic medicinal products (DIR Art 14), traditional herbal medicinal products (DIR Art 16a)[6]. Non-related adverse events, including serious events are not appropriate to NI studies. More often we still see the reporting of AEs written as part of the study protocol.

Perhaps that is because the Good Pharmacovigilance Practice (GVP) Module VI in the section *Reports from non-interventional studies* indicates that only reports of adverse reactions where a possible causal relationship with the suspected medicinal product is considered by the primary source or the marketing authorisation holder should be reported; other reports of events should be included in the final study report. Other reports of events' can be interpreted as AEs of Special Interest, those initially reported as ADRs that turn out to be non-related on review of the individual Case Report and non-serious expected ADRs which do not have to be reported to the competent authority.

There is a strong argument for removing the collection of AEs from NIS Protocols, that is compliant with GVP regulation July 2012 Module VI Reporting of Adverse reaction.

All standard pages, such as vital signs, medical history pages and laboratory pages should be reviewed. You may find that the same level of detail is not required in NI studies. The problem is usually that the Sponsor provides standard pages from early phase protocols rather than developing NIS standard pages. Developing standard NIS pages would remove the dilemma of whether this data should be queried or whether it is important or not.

> “We must strike a balance between data collection and burdening the clinical team or the patient. A well designed CRF, tightly reflecting the protocol, will also assist with this.

Rule 3: Think of the relevance of data queries.

NI studies should be easier for the clinical staff to administer than clinical trials. Asking clinical staff to resolve only data queries that are essential to the descriptive analysis is a good start.

More challenging perhaps is to think about the query and whether it is critical to their treatment decisions. Let's look at an example.

A product Summary Product Characteristics (SPC) specifies that a diagnostic procedure (MRI - Magnetic resonance imaging) is advisable within 90 days of deciding to prescribe a drug.

The observational data collected shows that often physicians are prescribing the drug without performing the diagnostic procedure within the 90 days. Perhaps they are using “older data”, from an MRI that was performed more than 90 days or other diagnostic evidence to make a treatment decision. We have data but not the data we expect.

Do we raise this as a query? Do you go back and tell the doctor that she/he is prescribing incorrectly or question the treatment decision? A data query may not be the best way to manage this. These are real world treatment decisions which may not always be conducted strictly in accordance with the Summary Product Characteristics (SPC). Perhaps if we have identified a clinic that is consistently outside of the recommendations then it can be a trigger for a representative to open a dialogue at that clinical centre. Sending queries for data that is valid but not expected may not be the best approach.

We must strike a balance between data collection and burdening the clinical team or the patient. A well designed CRF, tightly reflecting the protocol, will also assist with this.

NIS-DM Rule 4: Simplify the Query Process Flow

Resolving data queries is easier when there are less people involved. If the Data Manager and the clinic can communicate directly to resolve the query then we should keep the monitor/CRA out of the data-cycle. We can, of course, provide read-only access to the query for the monitor/CRA and allow the monitor to write “notes” (not considered queries or part of the data management (DM) process). Of course if the monitor/CRA wants to raise a query they should be able to advise the Data Manager of their observations so that the DM can consider this.

The query to be resolved should have minimal options, if possible. We would suggest just two: change the data or confirm it is correct.

NIS-DM Rule 5: Be “smarter” with edit checks.

With edit checks, one could consider the categorisation of data checks and plan how best to handle a query accordingly e.g. such data categories would include “mandatory and defined”, “of acceptable ranges and exceptions” and “laboratory data and significance”. Management of each category can be part of the NIS-DM plan.

For example, a scale such as the EDSS (Expanded Disability Score) can be mandatory in many Multiple Sclerosis studies. It is a well-defined scale i.e. all entries must be 1-10. Therefore with this mandatory/defined category we DO NOT ACCEPT other values; all other values are blocked using an edit-check at the time of data entry. No exceptions and no queries.

We have simple range checks which may produce exceptions. The simplest example of this is a height check. We can use the well documented, if slightly flawed, revised Metropolitan Life Height / Weight tables as an example[7]. These tables suggest that the heights of men (between 25 and 59 years of age) range from approx. 157.5cm to 193cm (5'2" and 6'4"). So, how do we handle a recorded value of 200cm?

We simply accept this as correct. We do not query it. It is a fact that an individual may have a height of 200cm. Again, if we see multiple patients who are very tall from a single clinic then we may want to discuss this but do not immediately raise a query for such data.

Laboratory values are always difficult to manage and frequently have multiple queries raised against them. Out of range values should not result in a query IF the field identifying the value as clinically significant/not clinically significant is completed.

"SMARTER" means understanding that it is real world data that we are collecting, which by its nature will be more variable than clinical trial data. Understanding this, we can categorise the data, allowing us to make an informed decision whether to raise a query or not. We must look at the context of the data to make decisions about whether the data has a good probability of being correct.

"SMARTER" also means looking at the data across sites and over time. Critical data can be compared between sites and over the course of the study. This will highlight any systemic issues with data collection and allow a corrective action or preventative action to be considered while the study is still operational.

Rule 6: Understand the analysis requirement of the protocol before writing a data validation plan.

The analysis section of the protocol is important. Data management personnel must understand what data is important to the statistician/analysts including what baseline data is required for the analysis. The data management plan must reflect these needs.

When a descriptive data analysis is required and no confirmatory statistics will be applied, it is equally important to work towards a clean data set to support the analysis.

Do not, however, employ the standard checks that are routinely used in clinical trials. Ask yourself "what can be eliminated from the standard list of checks?"

Equally important is to plan for missing data. Designing a CRF for use across centres or countries where the standard level of care will differ means that we will potentially have many more missing data points than in a clinical trial. Similarly, when a study collects retrospective data there will always be data missing from what is often defined as a core data set.

Evaluate and communicate the availability of key data elements which make up the core data set. The statistician/analyst must be aware of the decisions made around missing data and follow-up may not be an option.

Rule 7: Write an NIS-data validation plan

In effect we are recommending the same approach to the preparation of any data validation plan or data management plan. Do not add in "all the usual" rules. Do not just use the early phase template or SOP.

> "Equally important is to plan for missing data. Designing a CRF for use across centres or countries where the standard care of care will differ means that we will potentially have many more missing data points than in a clinical trial.

For example, in most situations its relevant to have a good classification of medications and diseases (by means of coding WHO-ATC or MedDRA). It is then important to ensure that all verbatim terms are legible. It is essential that the data manager understands the purpose of coding data and why it is performed. It may not be necessary in all studies e.g. in the case of a mature product, and if you choose not to code it can always be done at a later stage.

If you are considering such a move, it may be necessary to list what will NOT be checked to demonstrate that all data has been considered; this may be required until a new standard template for NI studies, in which your company has confidence, can be developed.

In conclusion

NIS specific standards and processes need to be developed. As we work through the process of data cleaning, it is important to liaise with data analysis and to understand the study report requirement. In many sponsor and CRO organisations the processes being used have been designed for clinical trials. While these processes are well defined and work well in the earlier phase studies they have, silently, added inefficiencies into the NI study phase. Standards in clinical trials should not be applied to the NI study plan.

We are working in an environment of standard care which differs across centres and countries and therefore we must adjust our processes to produce data of good quality. NIS can produce good results but it requires the processes that we use to be reviewed and adjusted.

Specific NIS standards and design should be part of this process, paying particular attention to those common events such as concomitant medications,

AE pages, medical histories; the pages that perhaps get less attention because they are omnipresent. If Sponsors continue to use clinical trial CRF design and utilise standard clinical SOPs for NI studies then we will continue to introduce inefficiencies into the system. Inefficiencies that we lose sight of and which continue to cost us in resource, effort and the good will of the clinical staff. Data collection must be well defined, limited and focused where possible. A good CRF is closely aligned with the primary objectives of the study.

Along with this we suggest the development of an NIS data validation plan incorporating some flexibility for review of data that may lead to decisions being made NOT to query real world data. Expect missing data and plan how to handle this. Rule writing can be simplified by creating and using such tools as rule builders which can remove any requirement for database programming. The majority of the rules required in NIS are common across all studies. Develop or use a tool that can write common rules quickly; this reduces the time taken and lowers the skill required. Include consistency checks across multiple sites and over the course of the study.

We need to be smarter in our approach to raising queries in NI studies. We should categorise the data if it helps in managing the decision of whether to raise a query against it. We should work towards less queries and towards understanding the context of the data captured. Have we supporting evidence to allow us to infer that the data is probably correct? Expect unresolved queries and plan how to manage these.

While a lot of these recommendation may be obvious, what is more obvious to us is that the same mistakes are being made across many studies by different stakeholders. So to enable robust, efficient NI studies, stop editing the current SOPs and instead invest time in writing new NI study procedures

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EUCROF, European CRO Federation

EUCROF, European CRO Federation, aims to promote clinical research and support the close relationship and exchange of information between member associations. The Federation develops training and educational programmes for clinical research and shares information on developments in clinical research with health care professionals at international level. EUCROF consists of members and associated members from 17 countries and stands for 300 member CROs and over 15,000 employees.

Late Phase Working Group

The mission of this working group is to promote good practices in the conduct of Late Phase studies, including observational and non-interventional through the sharing of knowledge, competence, expertise and skills. To be a recognised stakeholder among industry and regulators in the conduct of such studies in Europe and globally.

www.eucrof.eu

www.realworldedc.com

Clinical Trial Medication Adherence: From Guesswork to Data Point

Highly engaged subjects that consistently take their prescribed medications as directed are the cornerstone of a successful clinical trial. Yet, researchers have long struggled to effectively and efficiently validate adherence—relying on an arduous and often inaccurate combination of self-reporting and lab tests.

Today, advances in digital medicine, specifically the promise of ingestible sensors combined with electronic data capture (EDC) technology, are changing the landscape. Together, these powerful solutions enable more accurate and timely insight into medication adherence during a clinical trial. Obtaining this adherence data can enable good decisions regarding dosing selection and drug effectiveness, keys to reducing phase II and III failure rates and driving down their associated costs. In addition, this insight lets study managers obtain early warnings of poor compliance by subjects and sites to take quick corrective action or halt the trial early.

Eliminating barriers to success

One of the chief contributors to overall trial cost is the high failure rate of phase III trials, which are often hampered by incorrect dosage selection based on unreliable phase II dose-response results (Figure 1). As phase II dose-response studies assume all prescribed doses are being taken by all subjects in the trial, the key to improving dose-response results is to increase rates of medication adherence by improving the accuracy of data informing study designers of actual rates of medication adherence.

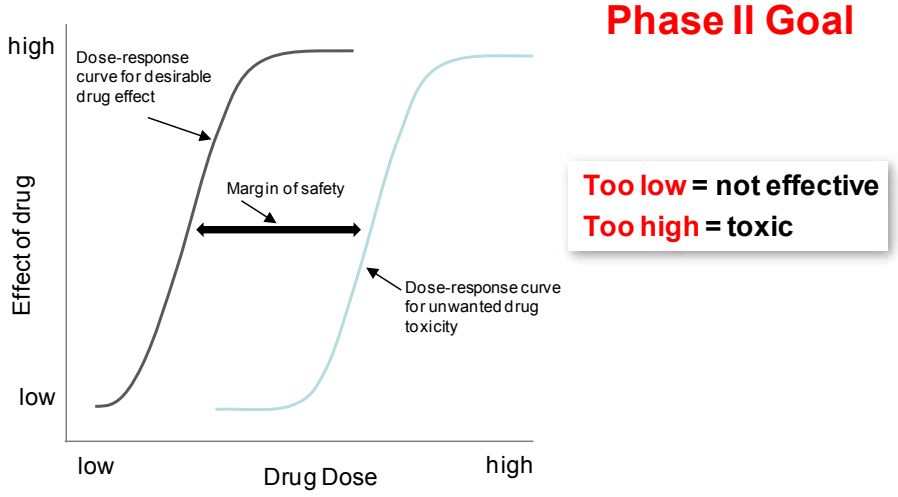
Sponsors and CROs are faced with the challenge of determining which subjects ingested medications prescribed during a trial, as well as whether doses were taken at the correct time and in the proper dosage. Inaccurate, incomplete, delayed, or missing adherence data severely limits researchers' ability to make informed drug development decisions.

Early in development, medication adherence data provide a foundation for making "go – no go" decisions. In later stages, adherence data impacts drug safety and efficacy decisions. For example, dose selection for phase III studies may be based on inaccurate assumptions from phase II trials.

While some costs associated with undertaking clinical trials are fixed (infrastructure and materials), others may be affected by adherence-related variables such as sample size, and length of time to complete a study. In addition, incorrect assumptions of adherence can increase the cost of resources such as medication provided, labs, personnel, number of tests performed, as well as the cost of undertaking trial monitoring activities aimed at improving rates of adherence (e.g., phone contacts, or direct observation).

Perhaps the most significant challenge to the goal of increasing adherence rates are the limited tools available today for adherence metrics, which only provide indirect measures or lagging indicators, and therefore uncertain estimates of actual drug intake. For example, pill counts, electronic pill boxes, questionnaires, or measuring drug concentrations provide uncertain estimates of adherence, often relying on assumptions rather than hard data. Statistical models, which are often used in determining adherence rates, are only as reliable as the accuracy of the data on which they are based.

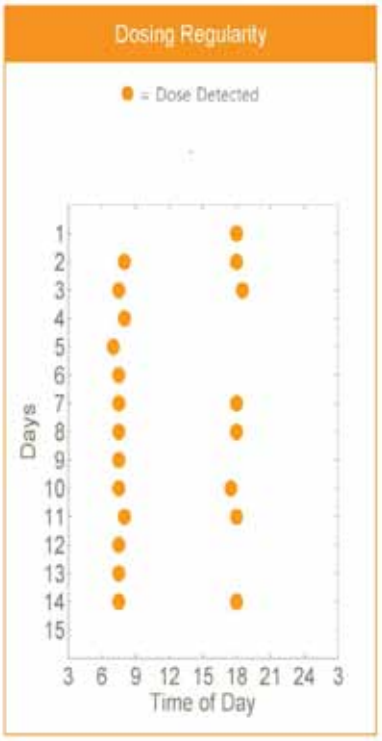
Figure 1: Dose-response curves in phase II impact dosing selection in phase III of trials



The digital revolution begins

To address these challenges, Oracle and Proteus Digital Health engaged

Figure 2: Gain insight into ingestion patterns of a trial subject / site



Cumulative Adherence, by Site and Subject

Cumulative Adherence, by Site and Subject

GREEN = Excellent YELLOW=Average RED = Below Average

Site Mnemonic	Subject Number	Cumulative Doses Ingested	Cumulative Doses Expected	Adherence
001	001001	99	124	79.8
	001003	62	82	75.6
005	005001	14	18	77.8
	005002	11	10	110.0
	005003	4	4	100.0
	005004	N/A	N/A	N/A
	005005	6	16	75.0
010	010004	N/A	N/A	N/A
030	030003	N/A	N/A	N/A
	030004	13	28	46.4
090	090001	7	6	116.7

in a strategic partnership, announced in 2013, to bring precision adherence and data capture together in an integrated solution.

Proteus Digital Health developed the world's first ingestible sensor that emits a pill-specific signal inside the body without use of a battery, radio, or antenna. Proteus has received FDA market clearance in the United States and a CE mark in Europe for its wearable and ingestible sensor devices. In a clinical trial the Proteus sensor can be over-encapsulated with the trial medication prescribed to the subjects. The sensor is activated by the body at point of ingestion and sends a unique ID code which can be used to identify therapeutic information such as type of medication, dose, and time ingested. This dosing data is then transferred, and combined with other clinical data, in Oracle Health Sciences InForm EDC platform providing immediate actionable insight into subject adherence.

From guesswork to data point – benefits of precision adherence

The combination of adherence data and EDC data, filtered by subject, visit or site provides study managers with deep, actionable, and current insights which can help to reduce monitoring costs while identifying critical distinctions between non-adherence and non-response (Figure 2).

From a monitoring perspective, study managers can quickly identify subjects with poor adherence who may need additional training, encouragement, or clinical consultation to reset their adherence to the regimen per the protocol. Likewise by comparing adherence across sites it is easy to identify which sites may need targeted monitoring to address adherence issues before there is an impact on key trial milestones.

As in Figure 1, this precision data can improve future study designs ensuring the optimal balance between safe and effective dose. Getting this right could help drive early market launch; getting this wrong could trigger significant research investment in a non viable product.

Summary

As sponsors and CROs face the continuing challenge of increasing the success rates of clinical trials, they seek new solutions that can generate timely and accurate data that precisely identifies medication ingested by each subject in a trial. Advances in digital health technology and electronic data capture platforms provide a new opportunity for researchers, and regulators, to rapidly optimize and deliver more effective therapies to patients.

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By Jonathan Palmer, Product Strategy, Oracle Health Sciences and Mike Lange, Product Strategy, Oracle Health Sciences

The Cost of Doing Business in the Cloud for Pharma

The focus of this paper is the "cost" of utilising Cloud-based services from the perspective of a CRO or Clinical services company. Such a company may currently be in the process of constructing or adopting a cloud-based software stack. What are the challenges they are going to face? This paper will address some of these concerns.

On the cost side, detailed monetary figures are not yet available. From researching this paper, reliable figures connected to the cost of utilising cloud-based technologies in a Pharma context were non-existent. The focus will be therefore on generic cost factors closely correlated with cloudadoption like data privacy and process re-engineering that apply in any industry.

The paper will then address issues specific to the Pharma, CRO and EDC vendor context, for example:

- What are the challenges facing the clinical process that Cloud Technologies might address ?
- What are the cost implications of tackling/not tackling these challenges?
- Is this a case of what we have is good enough, the costs are too high, the unanswered questions too numerous to justify committing precious resources to the job?
- Where the bite points might lie for the clinical process in adopting Cloud technologies?

I will also share Clinical Trial EndPoint (CTEP) experiences as a functioning CRO and clinical software innovator.

Introduction - the CTEP perspective.

CTEPs research has delved into industries where Cloud deployment is at a more advanced stage than in Pharma. Comparative costs for adoption of Cloud models and service strata therein were hard to come by but given Pharma's snail's pace migration to the digital universe, the Cloud will also take time to adapt to internal rigours and demands of Pharma regulation. CTEP's research has revealed that the likely costs to Pharma will come from process re-engineering, regulatory changes and generic factors such as skill shortage, data privacy that have a strong bearing on cloud adoption costs generally. Later in the paper I will bring a focus to cost factors specific to CROs, EDC vendors and their ilk.

Feasibility issues related to running clinical trials through the Cloud are not a cut and dry and it is CTEP's conclusion that under a strict regulatory environment, the adoption strategy will evolve only when key issues such as data location, privacy, safe harbour have been addressed. Even the Food and Drug Administration (FDA) has struggled to clarify what is acceptable practice when Cloud is combined for example with mobile technologies in a clinical research setting.

The Good Automated Manufacturing Practice (GAMP) guide to good manufacturing practice published by the International Society for Pharmaceutical Engineering (IPSE) [3] is a document at centre of all Pharma regulatory formulation. In light of the weight it carries, the organisation has as recently as 2013 set up a Cloud SIG [4] as a go-between for regulators and Cloud providers like Microsoft, VM Ware and Amazon. It is hoped that in future this initiative will result in ready-made Cloud solutions for heavily regulated IT while delivering on the Cloud promise of cheaper, elastic computing. Companies such as Montrium[5] are laying the groundwork for Cloud-based validation systems so the picture is one of colour gradually replacing grey but at a very slow pace..

> "Even the FDA has struggled to clarify what is acceptable practice when Cloud is combined for example with mobile technologies in a clinical research setting.

Complexity in Cloud Adoption

A key issue cloud adoption brings with it is "complexity":

- take an existing company with all software hosted internally
- all costs are known as is the bottom line.
- all processes are known and well defined
- all software – clinical and non-clinical -treated as one

In contemplating a shift to a Cloud-based technology stack, an organisation is faced with obstacles that may not have occurred to the originator of change:

- external hosting: security, validation and regulation
- cost control becomes more complicated, likewise identifying the bottom line
- processes may require adjustment or redesign from scratch

- some software may already exist as Cloud-ready, other more strategic software may have to be written using Cloud -based tools.

Those with the required skills for migration and implementation of the new environment will have to be found to tackle generic and Pharma-specific issues such as:

- **Data security –** the validation overhead required to satisfy a Pharma auditor or national regulator is currently a black box. Montrium[5] are a good example of a 21st Century organisation trying to sort out these problems.
- **Process management and re-engineering** in the area of data management where process inertia exists for very good reasons.
- **Software provider assessments –** do the existing Service Level Agreements (SLAs) cover Cloud-oriented software or is a case of new contracts and unforeseen changes and costs?

These three areas are at the core of "cost" accumulation in the transformation of traditionally hosted software stack and attendant applications into a Cloud-based equivalent. It is worth spending a little more time in each area to assess the pros and cons:

1. Data Security

Research data lives in a category of its own. Health Insurance Portability and Accountability (HIPAA) regulations cover medical record security but Pharma doesn't operate in that space from a data perspective so there are no specific guidelines on where clinical research data should be stored, who should have access to it and how long it can be kept in a Cloud context.

2. Process Management and Re-engineering

Pharma runs on a well defined set of SOPs with the laudable aim of producing safe products for market. Companies are put out of business for breaches of regulation or failing to adhere to their own SOPs. Inertia around change is as a consequence the norm and in the fast paced world of Information Technology (IT), tangible results can be very slow in coming.

> "All this change has also meant a shift in research focus. Clinical trials have had to become ever more nimble, cheaper to build and more user-friendly given the move away from the scientist and toward the doctor as the research agent.

3. Assessment of software vendors

Fit for purpose software is close to the top of every purchaser's assessment list. With a new environment like the Cloud, has existing, pre-validated software been migrated to operate in the Cloud or will it be a question of new products from new vendors ? The regulation and validation overhead will differ greatly depending on the answer given to this question.

Clinical trials is a specialised area of software development so availability and costs of Cloud deployable software might boil down to a choice of (for example)

- Oracle (phase I-III) if already an Oracle house,
- Medidata (phase I-III) Cloud enabled
- RealWorldEdc (phase IV, registries, post-marketing) Cloud enabled

Holy Grail

The Grail for a clinical process is one that adheres to all regulations, is fit for purpose and provides the Cloud "pay-as-you-go" elastic computing model on the cost front. It has worked in other areas of corporate software-as-a-service like email, Clinical Research Management (CRM) and even basic Office-style productivity software. Why couldn't this model deliver the promised cost savings for building, deploying and managing clinical trials in the Pharma world?

There are hiccups as alluded to previously. Recent experiences in CTEP's external auditing processes suggest that "finger on the metal" remains a requirement for a clinical trial data set. What this means in essence is the database must always remain under the control of the vendor, in this case CTEP. Pushing the data store into a public Cloud like Amazon or Azure will never be feasible and even the provision of a private Cloud infrastructure in a data centre will be subject to rigorous application of this metric. Standards of data practise like HIPAA do not yet exist for Pharma so there remains a grey area.

Out of necessity, CTEP use a hybrid form of Cloud provision to deploy clinical trials which fractures the Cloud delivery model and adds complexity and cost rather than reducing them. The promise of the Cloud is ostensibly turned on its head tarnishing the Holy Grail almost before it has had time to rise.

A Market Ready for Change

But why even go down this route of moving the clinical development process to a Cloud based environment?

There are a number of factors on the Pharma side that make it a worthwhile goal even with the outlined downsides. The rate of business change in Pharma has sped up massively in the last decade

- blockbuster drug pipelines have dried up
- mergers of the largest companies is shrinking the market and reducing the likelihood of new compounds being discovered
- a renewed focus on market-led development

All this change has also meant a shift in research focus. Clinical trials have had to become ever more nimble, cheaper to build and more user-friendly given the move away from the scientist and toward the doctor as the research agent. Add to this mix the advent of mobile technology as well as the Cloud, and a market ready for major change has emerged.

The change has brought stresses but also the space for innovation.

The focus on Cost in Pharma

Clinical research organisations (CROs) and research managers are increasingly taking a closer look at the actual costs associated with software for trials.

To use a well-known system such as Oracle's Remote Data Capture (RDC), the following softwarestack is required:

1. Oracle Relational Database Management System (RDBMS) database
2. Oracle AppServer/Fuse/Glassfish
3. Oracle Clinical
4. Oracle RDC.

It comes to a lot of investment so project managers and clinical trial investors are beginning to ask:

'What is the unit cost of using this software stack and what impact does each study's customisation have on the overall cost of a clinical trial?' This question is especially relevant to late phase and post marketing studies.

Longer-term, they may ask what sort of research pipeline is required to ensure this investment pays for itself within X-number of years. Then they have to factor in how often each of these orthogonal products has to be upgraded to a new version? Then there is training, consultancy, repeated licenseto-own-per-end-user costs etc. Overall, the costs attached to investment in a major clinical trial software stack are massive [significantly over €100,000 – and rising]. It's a gravy train for the vendor and a major headache for a CRO or pharma company looking to cut back on overheads.

This is where non-Enterprise solutions and systems come into play especially in lower cost late phase and observational studies. The use of the Cloud as a delivery platform plus an increasing emphasis on standards-based processes and tools end-to-end will provide an alternative. But concerns remain that these alternatives, albeit providing better value, may not be up to clinical research standards especially for reliable and efficient data capture.

This is where the international the **Clinical Data Acquisition Standards harmonization (CDASH)** takes a leading role. It is a ***non-profit organisation***, whose mission is "to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of health-care".

The CDISC data standards as defined are a set of interlocking naming conventions and data models, which can be deployed in an electronic format. The preferred electronic format is XML. Using the Operational Data Model (ODM) as a carrier, naming standards such as SDTM, Clinical Data Interchange Standards Consortium (CDASH), Analysis Dataset Model (ADAM) etc. result in a data processes developed, deployed, stored and analysed in a universal language.

CTEP (Clinical Trial EndPoint) ***www.realworldedc.com*** provide one of the more popular, lowercost options which is also fully compliant and accredited with CDISC standards, The customer "rents" the use of Cloud-hosted Assembler/ Builder services plus a fixed development license (up to ten in a bundle) plus a monthly rent for every live study. The customer can build their own portal for each study and CTEP provide additional services such as an online validation process, global rule builder as plug-ins to the standard model. This avoids the high 'big-brand' software and licensing costs which have dominated clinical trial budgets in the past decade.

> "CDISC's mission is "to develop and support global, platform-independent data standards that enable information system interoperability to improve medical research and related areas of health-care".

The future of software delivery is premised on a migration of suitable services to software-as-a-service (SaaS)-based, Cloud-resident services where an existing business model – such as clinical trial infrastructure – can be adapted and streamlined to suit the customers requirements. Without additional IT overhead associated with on-premise or application service provider (ASP) models of delivery, major savings can be envisaged provided this new environment can be made to work in the pharma context.

Cloud and SaaS Proposition

CTEP's research into the delivery of standards-based clinical trial services sees this new business model as the future especially for post-marketing/ phase IV & observational trials albeit with some adaptations of a pure SaaS model. The strict regulatory requirements guiding clinical software development mean customers cannot "share" the same copy of the Builder/ Assembler. Neither can the clinical trial data be stored in some randomly located database.

Without compromising on data security, patient safety or confidentiality, delivery of software using CTEP's Hybrid SaaS model will have immediate cost savings for vendors like CTEP and more importantly for CTEP's customers. The applications are purely cloud based while the databases remain under CTEP/

Figure 1: The comparison between the three different delivery models

	Internal IT	Managed Services (ASP)	The Cloud
Capital Investment	$40,000	$0	$0
Setup Costs	$10,000	$5,000	$1,000
Monthly Services	$0	$4,000	$2,400
Monthly Labour	$3,200	$0	$1,000
Cost Over 3 Years	$149,000	$129,000	$106,000

Data Managers' control. This cloud hybridisation is invisible to the customer while keeping the process on the right side of regulatory requirements. The result for research managers is faster delivery of lower-cost trials and an increasing awareness that expenditure on traditional enterprise, self-hosted software stacks will be considered wasted investment.

Costings

Key point to remember is that cloud computing shifts an IT company's expenditure profile away from capital investment in hardware and infrastructure to a utility-like service akin to electricity or phone system. Its also different in that scalability is built into the pricing model, the more cloud used the higher the rent, the lower the use the lower the rent and so on.

Use of cloud-based systems is not free but its certainly lower, more flexible and importantly it's a different kind of expenditure that has implications for company's tax bill.

Figure 1 shows the comparison between the three different delivery models [2].

So there are cost advantages to be gained for Pharma in Cloud adoption but where are the sweet spots? What factors specific to the clinical trial space could benefit from immediate Cloud adoption without having to wait for regulators to sort out what is and isn't appropriate at the global level.

The three factors selected are those in which the innovation cost of adopting Cloud technologies will bring dividends to data managers and IT staff at coal face of clinical trial operations.

1. Capital Investment (Iaas)
2. Software development (PaaS)
3. Software service buy/lease (SaaS)

> "The industry will still be faced with the same data management issues as currently but shifted into a different physical space. But where it will see benefits are with scaling, focus on core business (clinical not IT) and pay-as-you-go.

1. Capital costs in the Cloud era have been transformed into utility costs much like electricity or water. This may already be the model in other non-clinical areas of Pharma so the environment may already have softened up to this notion. Hardware and software maintenance costs all shift into the realm of a utility cost. In Cloud stack terms, this is the Infrastructure as a Service (IaaS) layer.

2. The software development platform is the development kit for pushing out new software. There are many options in this area also known as Platform as a Service (PaaS). It is a key area of change for anyone with a vested interest in services that support software development. Some key areas of consideration CTEP have had to address are (1) location of database (2) pay as you go in development cost (3) multi-tenant versus single tenant (4) web service integration as a key for smooth adaptation of existing processes to new environments

3. Software service lease/buy is the SaaS layer that sits on top of the other two layers. The services are ready-to-use, modular , paid for on an hourly/daily/monthly rate. Applications delivered in this layer have limited reconfigurability and cannot be customised. The applications have scalability, load balancing and fault tolerance built in. The latter are amongst key reasons

CTEP's customers have highlighted in their expectations of moving to a Cloud based clinical trial service.

Change is implicit in migrating a technology stack to an IaaS/PaaS/SaaS model but once the dust has settled, the same core questions will be asked of whatever processes emerge:

- ***Is my data secure ?***
- ***What are the implications for process management /SOPs ?***
- ***What are the SLAs of the service providers and how do they impact on my ability to control costs ?***

I believe the cost of innovation for Pharma is too high due in part to the blockers imposed by the industry on itself. Also the reluctance to embrace change is endemic in the industry for well founded reasons. So there is no panacea here.

The CTEP Experience

CTEP have EDC, Clinical Trial Management System (CTMS) and Study Builder applications deployed in a Cloud environment. Prior to Cloud adoption, a new server was purchased for every three studies. There was a lot of non-Clinical overhead to be managed and the company looked for a way to reduce this.

The deployment model is configuration over customisation. It keeps the validation overhead low, turnaround time much faster which in turn means the customer is happy with the final

deliverable despite the reduced number of freedom degrees at design time.

The Cloud model is, out of necessity from audit outcomes, a hybrid Cloud model. The database servers remain under CTEP administration control from hardware on up. The application servers are Cloud-based. As a result, end user cost is higher than it could otherwise be in a pure Cloud environment. As an alternative, CTEP could build a private Cloud environment where all services reside together in a single logical domain but this option would require significant investment.

Cloud Stack Fit

As an EDC vendor, adopting an IaaS strategy had the biggest benefit. The Study Builder fits into the PaaS layer with the completed clinical trial deployed in SaaS mode. The latter two applications require further engineering before they can be classed as fully Cloud-ready.

Pragmatic

Often times, a clinical trials design requirement necessitates a wandering from the ideal implementation strategy and one advantage of a Hybrid Cloud model is its flexibility in the face of business demands without destroying the integrity of the product. As an example, an image loader was required in one trial and the business would have gone elsewhere if such a level of customisation had been turned down. In business, it is necessary to take the pragmatic approach to service provision even when the architect says otherwise !

Pay-as-you-go

It has nor been possible so far to introduce elastic computing into the model at the PaaS and SaaS layers due to customer expectations. The rental model at the IaaS layer has allowed CTEP as Cloud customers themselves to reduce costs that impact indirectly on our Clinical customers.

Late Phase clinical trials based in the Cloud are CTEP's speciality so the training overhead in terms of migrating existing clinical software services was not an issue.

The data centre hosting CTEP's own hardware built their own Cloud environment making the switch to IaaS cost effective despite the Hybrid model. CTEP did not as a result have to construct their own private Cloud.

Rebuilding the software to make use of new pathways in a PaaS has been the most time consuming task of all and is a work in progress. The finished product is deployed using SaaS and that has been successful.

Conclusion

There is no panacea in the clinical trial space where Cloud utilisation is concerned. The industry will still be faced with the same data management issues as currently but shifted into a different physical space. But where it will see benefits are with scaling, focus on core business (clinical not IT) and pay-as-you-go.

Currently, there are blockers to innovation such as location of data. So cost savings will accrue gradually as the regulatory frameworks catch up with the technology innovations. Migration and re-engineering costs will take time to absorb but in future, all clinical services will end up in the Cloud so finding the way to make it work remains a worthwhile goal.

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Incorporating Biomarkers in Clinical Trials: Data Challenges and Best Practices

Among the expected benefits of incorporating biomarkers in clinical trials are the accelerated development of new personalised therapies and medical diagnostics, while enhancing patient safety and reducing Research & Development (R&D) cost. However, the use of biomarkers in a regulated environment is creating its own set of practical challenges, especially around how to effectively collect, manage, and analyse genomic data in a trial. In this work we discuss these challenges and propose approaches for the inclusion of biomarkers in the clinical development program.

Introduction

Today, most clinical trials are designed to address the patient population identified by a specific disease. In practice, even most of the successful trials have large cohorts of non-responders, who experience the adverse events of the treatment without enjoying the benefits. For example, four in ten patients treated with anti-arrhythmic drugs don't respond to therapy [1], while still being exposed to a wide range of side effects, including worsening of arrhythmias.

This lack of effectiveness is clearly a concern for healthcare organisations, both for the poor patient outcomes as well as for its economical consequences. In response, new trials have emerged which attempt to segment the patient population based on biomarkers that are likely to identify responders.

Clinical practice already includes biomarkers, as in the example of protein levels for liver function (e.g., transaminases, bilirubin, alkaline phosphatase) which are standard lab tests. It is however a new category of biomarkers, the so called "OMICS", that industry and academia are hoping to leverage, in the attempt to identify responders. Genomics, proteomics, epigenomics, all offer a vast, diverse and still mostly unexplored set of data, unique to each patient. Hope in this novel approach comes from success stories such as ivacaftor, a therapy for cystic fibrosis which was approved by the FDA in 2012, after a three-month Phase III trial with as little as 161 patients [2].

Dealing with biomarkers brings challenges to clinical organisations, especially when the objective is to integrate these biomarkers within the framework of regulatory submissions, with standard operating procedures typically more restrictive than those adopted during drug discovery. We worked with organisations which are investing in these new trials, and here below we discuss the common challenges they face as well as approaches we have taken to help them cope with these challenges.

Data challenges

In our work with organisations that intend to include biomarkers in their clinical trials, we have identified several challenges, including:

- acquiring, normalising, and combining clinical trial, OMICS, and other real-world data
- operating across studies and silos of information
- managing petabytes of OMICS data and ensuring real-time information queries
- maintaining interoperability between open source and enterprise software
- collaborating in the cloud while ensuring HIPAA compliance
- meeting regulatory requirements for submission

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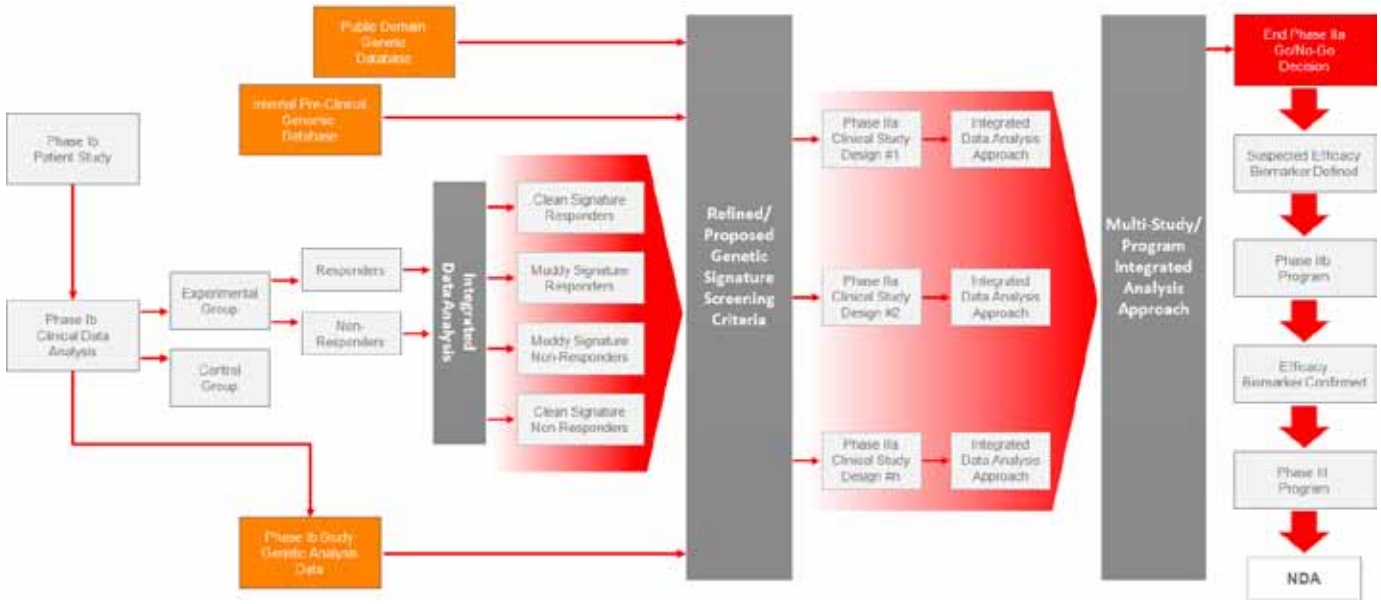
A more detailed discussion on these challenges is publicly available [3]. Organisations willing to venture in new trials need adequate infrastructures and partners, as the traditional clinical trial model which separates drug discovery from clinical evaluation is prone to operational delays and failures which may jeopardise the fair assessment of a treatment and its companion biomarker.

Including biomarkers in the clinical development program

We have worked to help organisations incorporate biomarkers in their clinical trials. Figure 1 illustrates this process.

After Phase I, sponsors assess safety of the treatment on the whole patient population, and collect preliminary outcomes on efficacy. Next they need to integrate the available clinical data with their internal data on biomarkers and with public, annotated datasets. For most organisations, this proves to be a difficult task, with bioinformaticians

Figure 1. Example of a clinical development program which includes biomarkers.



spending most of their time in combining the data, manually tracking which version of datasets were used, and with scientists waiting for data and analysis to be ready before formulating new questions. This usually leads to a new cycle of data aggregation from the bioinformatician, a new evaluation from the scientists, and so on.

We engineered a system that automatically aggregates data coming from different data sources, scales to the large volumes of OMICS, and keeps the versioning of the originating data sources. Data is aggregated in a robust, extensive and standardised data model. Queries implemented with the system (e.g. "All female patients with mutation X who had cancer relapse") execute in seconds and can be saved and shared between bioinformaticians and scientists. The aggregated data model and selected cohorts are available to downstream applications (e.g. R) for analysis. The security model ensures users only access data they are allowed to, based on their group (e.g. cardiology, bioinformatics, ...), to preserve compliance.

Although clearly still hypothesis generating in nature, the results obtained after Phase I are instrumental in designing Phase II studies. The putative biomarkers are included in Phase II trials, most likely as secondary and tertiary objectives. The outcomes observed in the Phase II studies may be pooled to increase the sample size for each subgroup, and the OMICS data collected on the study patients can be aggregated with public annotated datasets. If the stratification of the original patient population on the candidate biomarker achieves a significant difference from placebo with a meaningful effect size, organisations may decide to design a Phase III study (confirmatory) where the biomarker and its companion diagnostic test are used together with the therapy to define the inclusion criteria and to assess the effectiveness of the treatment in the patient population associated with the biomarker.

Including biomarkers in Phase III trials means that now the OMICS data has to comply with regulatory requirements for submission. This includes HIPAA compliance, access control, version control, audit trails, and more requirements which are usually not enforced in the pre-clinical phase. To this extent, we have built an integration of a leading EDC system with OMICS data. This integration is covered by the same layer of security, validation and processes that are in place within the EDC system, commonly used for regulatory submissions. This enables organisations to incorporate their biomarkers in clinical trials in a compliant manner.

Conclusions

Clinical organisations are increasingly adopting biomarkers in their clinical trials. These new trials promise benefits for the patients, with more accurate identification of responders and therefore less unnecessary exposure to drugs and adverse events; and benefits for the clinical organisations, including smaller Phase III trials and faster approval. The challenges are larger data volumes, high heterogeneity of sources and formats, and the need for increased collaboration while meeting demanding regulatory requirements. We have worked with organisations that invest in new trials, and built systems to enable inclusion of biomarkers in the clinical development program. The supported processes include aggregation of

clinical, OMICS and public data, to a standardised data model; query engine that provide fast insights leveraging large amount of data, where results and query criteria can be saved and shared within the organisation; secured access; and integration of OMICS with EDC for confirmatory trials.

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System Validation (TrialMaster) – The importance of being compliant

Although System Validation has been discussed in our industry for more than 30 years, there are still companies out there who do not understand the importance of system validation and do not understand the consequences of not being compliant.

Validating the systems used in clinical trials and keeping the validated state (remaining compliant during the whole system life cycle) is crucial for companies in our industry. That means that it is not enough to validate your systems; you must also ensure that you have systems in place to handle changes to the system. Quality is commonly defined as fitness for purpose. Clinical research is about generating information to support decision making while protecting the safety and rights of participating subjects. The quality of information generated should therefore be sufficient to support good decision making. Unfortunately, during the last couple of years we have seen a few companies ignoring this system validation discipline; they are no longer in business.

The scope of Larix's presentation was first of all to provide information about the importance of being compliant.

Why it is Important to be Compliant:

- It makes good sense to be compliant for both a regulatory and business point of view as if not.....
- Consequence: worst case scenario: You might not have a business after an audit or inspection
- System Validation is a discipline.

A Risk Based Approach to System Validation:

Quality is commonly defined as fitness for purpose. Clinical research is about generating information to support decision making while protecting the safety and rights of participating subjects. The quality of information generated should therefore be sufficient to support good decision making.

Risks might be acceptable if they have limited impact on a subject's safety and rights - and limited or no impact on data integrity and reliability.

It is also very important to share some knowledge regarding how to be in control of changes (change management).

The system must remain in a validated state during the whole system life cycle. It is not difficult to validate a system, the difficult thing is to remain in a validated state and remain compliant during the whole system life cycle, especially if you are not in control of all validation activities, e.g. use subcontractors for hosting of data – how do you control changes performed by the vendor?

Drawbacks of non-validated systems:

Neither the system nor its outcome can be relied on as:

- There is no control over the system
- There is a risk of electronic data corruption
- The consequences of changes are unknown
- There is no control over risk factors.

No conclusions can be based on the results produced by a non-validated system. Both the data produced and the system itself can be disqualified during a regulatory inspection/audit.

Implementation of TrialMaster at Larix:

Larix validated and implemented TrialMaster (Vendor: OmniComm Systems) v.4.2 November 2014.

The scope of this project: Validate and document TrialMaster components, training of validation project team members, review and update SOPs and re-training of staff after SOP updates.

The first trial set-up in TrialMaster was performed in close cooperation with OmniComm Systems and part of this trial set-up was included in implementation and validation activities.

Project deliverables (validation package):

- Project Time/Action Plan - Larix & OmniComm Systems
- Complete Change Request
- Validation plan
- Create User Requirement Specifications (No URS no validation)
- GxP Risk Assessment, Traceability Matrix, UAT (User Acceptance Test) documentation.
- Validation report

Knowledge sharing regarding validation and implementation of a Data Management System in cooperation with vendor (OmniComm Systems) has been very valuable for Larix.

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