

Utilising STAMP to define the First-into-Man system for medicines

Dr Brian Edwards

Vice President Pharmacovigilance and Drug Safety

Alliance Clinical Research Excellence and Safety

brian.edwards@ndareg.com

Abstract: The (so-called) pharmaceutical safety system is struggling. Part of the problem is failure to define the complexity of the system and design processes which are evidenced based and both adaptable and flexible for those who work in them. The size of the challenge is huge and global. This is why ACRES (Alliance Clinical Research Excellence and Safety) was established as a not-for-profit international organisation to develop a global system for clinical trials, responsibly conducted according to the highest standards of safety, quality and efficiency as this currently does not exist. When defining the safety system for clinical research into medicines where do we start? ACRES suggests examining and defining the current safety system for how medicines move from the laboratory into man applying the STAMP model. This has never been done which is why the influence of some stakeholders on safety remains unknown. The aim is to build on what we know about the scientific evidence, current legislation and regulatory guidance underpinning pharmacological and regulatory science in pharmaceuticals. We aim to build a multidisciplinary team including safety engineers. This includes working with pharmaceutical professionals with different expertise and safety engineers with experience in applying STAMP from both the EU and US to map out the system using STAMP.

1 Introduction to ACRES and its rationale

The Alliance for Clinical Research Excellence and Safety (ACRES) aims to transform the world of clinical research so clinical trials are more responsibly conducted according to the highest standards of safety, quality and efficiency. ACRES is a not-for-profit organization whose leadership is comprised of experts in health policy, pharmaceutical

development and safety, academia, research sites, patient advocates and the ethics community. No such organisation exists with the intent of better defining and implementing a global system for clinical research. In order to effectively manage risk, it is essential to have an agreed definition of what the ideal system should be for the safe development and life-cycle management of medicines and yet this does not exist. The system for developing medicines has never been mapped out systematically to define all risks and hazards. Identifying all stakeholders who impact risk management has never been performed. We were influenced by an analysis of the US post-licensing system performed using Systems Theoretic Accident Model and Processes (STAMP) methodology [LCT13]. The STAMP model may offer an opportunity to do just this in an international setting. This because the guiding principles of Good Clinical Practice (GCP) underpins all intervention a research with medicines in humans [EMA12], [ICH 96], [FDA 13], [DoH 01], [FDA 06], [MHRA 13]. We propose as a first step, the examination of the early phases of drug development to determine if the implementation of improvement tools from organisational science (such as STAMP) can make a significant impact on safety. By STAMP treating safety breakdown as a control problem, not a failure problem, we can more logically design constraints on component behavior and interactions. This approach requires applying additional evidence from human factors research and safety culture so that we can better define how all the different players in clinical research interact and control safety within the system.

1.1 Why is such an approach needed?

Currently clinical research is based on application of regulations to pharmaceutical science:

- Too often regulation for clinical research are reactions to safety issues rather than being prospectively designed based on evidence
- Regulations stress compliance to systems and processes rather than prioritizing the avoidance of potential harm to human subjects.
- Regulations are added by different regulators without a holistic view of how they impact the system
- There have been no known attempts to apply organisational science techniques such as human factors with little attention to human performance analysis to identify and mitigate risk.
- There is no agreed Clinical Development Accident terminology.
- There are concerns about less than rigorous methodology and compliance in less regulated territories
- There are concerns about volunteer remuneration, lack of informed consent, informed consent under duress, coercion

- Drug development decisions are highly influenced by economics: market forces, commercial considerations, available capital. As a result, clinical development is often an exercise in risk aversion rather than risk management; as a result, many promising therapies are never developed.

In effect, we do not know what the system for moving medicines from bench into man looks like and what the systemic factors are for managing risk and there is no standard conduct for administering products for the first time into Man. Expertise outside of Biomedical R&D is crucial to success to creating a safety culture in our business sector.

2 Outline of the project

This novel ACRES project will examine First-into-Man (FIM) Clinical Research including early phase clinical trials (Proof of concept programs) to:

- Identify current system components, strengths and improvements that can be made in the safety activities of research at this phase.
- Review the regulatory framework, role and relationships in this phase of clinical development, adapt to a systems model and identify potential changes that may be required.

Various approaches and methodologies may be used in examining the system of clinical research in the FIM phase to identify its core issues and strengths as well as identify who are the stakeholders who influence safety. This will enable us to better utilize available safety engineering approaches, such as STAMP, in the examination and evaluation of system strengths and weaknesses, as well as their root causes which often relate the Human Factor. This way safety constraints can then be designed to design a more logical and scientifically satisfying system for managing risk.

2.1 Objectives and results which might be expected

2.1.1. Complete a fully defined system ‘map’ of the various components of the FIM Clinical Research including early phase clinical trials.

2.1.2. Apply available approaches, including STAMP, to examine this part of the overall clinical research system to determine:

- a. System strengths including identifying who are the influences on safety
- b. System failures defined in depth in accordance to the STAMP methodology
- c. Define what system accidents need to be prevented
- d. Propose system changes

e. Identify expected or possible difficulties with applying STAMP and develop solutions, if possible. During the workshop expected and possible difficulties in implementing the plan and applying STAMP to address the systems deficiencies will be discussed.

Expected difficulties by designing a theoretical system rather than one based on real life data (which would be commercially sensitive and unlikely to be made available) are as follows:

- Lack of information or inaccurate information especially based on what we would like to happen. Indeed, we have to assume that all in the system are agreed on the objectives of clinical research into medicine
- Variability within a process often is not defined or agreed
- Intrinsic pharmaceutical uncertainty in developing a new medicine making it difficult to define safety control actions
- There may be multiple process controllers
- Impact of inaction and organisational silence on managing risk is uncertain
- The environment in which controllers operate may be variable and difficult to define

3. What is required for this project?

To conduct a project of this type will require various types of expertise and a range of professionals as follows:

- Project Manager (pharmaceutical industry preferred)
- 10-12 Varied pharmaceutical professionals with experience in early phase research and safety for workshop with two moderators
- Lead STAMP Expert(s) for conduct of STAMP methodology and approach
- Graduate students to conduct interviews and document review

4. References

[LCT 13] Leveson, N. Couturier, M. Thomas, J. Dierks, M. Wierz, D. Psaty, B. Finkelstein, S. Applying System Engineering to Pharmaceutical Safety Journal of Healthcare Engineering Vol. 3; No. 3, 2012 pp. 391-414

[EMA 12] Reflection paper on ethical and GCP aspects of clinical trials of medicinal products for human use conducted outside of the EU/EEA and submitted in marketing authorisation applications to the EU Regulatory Authorities EMA/121340/2011 16 April 2012

[ICH 96] Guideline For Good Clinical Practice ICH 6(R1) Current Step 4 version 10 June 1996

[FDA 13] Oversight of Clinical Investigations — A Risk-Based Approach to Monitoring U.S. Department of Health and Human Services Food and Drug Administration August 2013

[DoH 01] The revised Declaration of Helsinki: interpreting and implementing ethical principles in biomedical research International Journal of Pharmaceutical Medicine 2001, 15:131–143

[FDA 06] Exploratory IND Studies Food and Drug Administration Center for Drug Evaluation and Research (CDER) January 2006

[MHRA 13] Clinical trials for medicinal products: Phase 1 Accreditation Scheme v.2 October 2013
<http://www.mhra.gov.uk/Howweregulate/Medicines/Medicinesregulatorynews/CON2033112>