The Power of Words – "Clinical Study"

"With great power, comes great responsibility" … as said by Peter Parker's Uncle Ben in Spiderman

Summary: According to ICH GCP, the terms clinical trial and clinical study are synonymous (as per Section 1.12 of ICH E6(R2)). The terms 'clinical study' and 'clinical trial' are not the same:

"According to the FDA, an observational study is a non-interventional clinical study design that is not considered a clinical trial; and according to the EU Clinical Trials Regulation, a non-interventional study is a clinical study other than a clinical trial"

The impact of grouping them together is far reaching and deconstructive. According to Albert Einstein, the definition of insanity is doing the same thing over and over and expecting different results…I know from first-hand experience that we can submit the **same** study type to IRBs/ RECs and competent authorities and get **different** results. Insanity? If the regulatory definitions are unclear or without regulatory context/ guidance, it's just as difficult for the regulators to implement as for the researchers to understand.

Let's keep things simple. Let's get back to the first principles of regulatory compliance. In order for us to comply with the regulations we need to **understand** what we are being asked to comply with = Give us more meaningful and actionable definitions. Give us case-studies. A regulator that does this very well is the MHRA (I'm in the UK so I'm biased – just saying).

What is a clinical study?

According to the clinical trial 'Bible' (ICH E6), a "CLINICAL STUDY" is:

Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous (as per Section 1.12 of ICH E6(R2)).

Seems simple enough!

This is indeed a simple definition…until we consider the last sentence = "The terms clinical trial and clinical study are synonymous"

I have to confess that I needed to look up the word 'synonymous'. It's a big word I don't tend to use in my day-to-day work. According to the Heinemann English Dictionary:

- Synonym (*noun*) = A word with the same or similar meaning to another *e.g., Happy is a synonym of glad*
- Synonymous (*adjective*) = Expressing or suggesting the same idea: These two words are synonymous *e.g., Our company's name is synonymous with good value*

Are the terms clinical trial and clinical study really synonymous?

According to the FDA, an observational study is a non-interventional clinical study design that is not considered a clinical trial (as per Glossary of Framework for FDA's Real-World Evidence Program - Dec 2018); and according to the EU Clinical Trials Regulation, a non-interventional study is a clinical study other than a clinical trial (as per Article 2.2(4) of Regulation EU/536/2014 – Refer to Table 1).

If you are an organisation or researcher running clinical trials this will probably have little or no impact on you. However, consider those of us who support and manage clinical studies that are not clinical trials e.g., disease registry studies, non-interventional studies, time and motions studies etc. Our studies are NOT the same or even similar to clinical trials when it comes to the regulatory requirements. For a start, we aren't governed by regulations that have their basis in ICH GCP. So, why add terminology to a guidance document for clinical trials that causes confusion, misdirection and horror to those of us who already have our hands full trying to get low/minimal/no risk clinical research studies approved by IRBs and RECs?

The plot thickens…the proposed new title for ICH E8 (General Considerations for Clinical Trials) is "General Considerations for **CLINICAL STUDIES**". Worse still, the revision broaches the topic of "INTERVENTION", without defining what is meant by intervention? Why is this a problem? If you are reading this and you design, support or run clinical studies that are not clinical trials, you will know and understand (painfully) the confusion that often comes with trying to understand if/when an intervention makes a non-interventional study, interventional….AAAGGGHHH! The pain! My head hurts!

Get to the point Stuart!

The terms 'clinical study' and 'clinical trial' are not the same. The impact of grouping them together is far reaching and deconstructive. It causes confusion at the study design, approvals/submissions, conduct, and reporting levels. According to Albert Einstein, the definition of insanity is doing the same thing over and over and expecting different results. As someone who provides regulatory guidance for clinical studies that are not clinical trials, I know from first-hand experience that we can submit the **same** study type to IRBs/RECs and competent authorities and get **different** results. Insanity? If the regulatory definitions are unclear or without regulatory context/ guidance, it's just as difficult for the regulators to implement as for the researcher to understand.

My ask? Let's keep things simple. Let's get back to the first principles of regulatory compliance. In order for us to comply with the regulations we need to understand what we are being asked to comply with = Give us more meaningful and actionable definitions. Give us case-studies. A regulator that does this very well is the MHRA (I'm in the UK so I'm biased – just saying).

Thoughts?...

Table 1 - Terms and Definitions in the Context of the EU Clinical Trials Regulation*

Term	Definition	Context
Clinical Study	'Clinical study' means any investigation in relation to humans intended: (a) to discover or verify the clinical, pharmacological or other pharmacodynamic effects of one or more medicinal products; (b) to identify any adverse reactions to one or more medicinal products; or (c) to study the absorption, distribution, metabolism and excretion of one or more medicinal products; with the objective of ascertaining the safety and/or efficacy of those medicinal products >>as per Article 2.2(1) of Regulation EU/536/2014	There must be a **medicinal product** for this to be a clinical study in the context of this regulation. So, we know that this regulatory definition does not cover clinical research where there is no medicinal product e.g., disease registry studies.
Clinical Trial	'Clinical trial' means a clinical study which fulfils any of the following conditions: (a) the assignment of the subject to a particular therapeutic strategy is decided in advance and does not fall within normal clinical practice of the Member State concerned; (b) the decision to prescribe the investigational medicinal products is taken together with the decision to include the subject in the clinical study; or (c) diagnostic or monitoring procedures in addition to normal clinical practice are applied to the subjects. >>as per Article 2.2(2) of Regulation EU/536/2014	There must be a **medicinal product** for this to be a clinical trial in the context of this regulation. So, think about this… what is a clinical research study in which patients are subjected to liver biopsies (physical interventions) and which does not involve a medicinal product? Is it a clinical trial, in the context of this definition?

Term	Definition	Context
Non-Interventional Study	'Non-interventional study' means a clinical study other than a clinical trial >>as per Article 2.2(4) of Regulation EU/536/2014	There must be a **medicinal product** for this to be a non-interventional study in the context of this regulation. Oh…but don't forget that the regulation that defines what a non-interventional study is, also derogates any responsibility to governing the clinical study type that they've just defined with an 'anti-definition' i.e., the regulations tells us what it is not, rather than what it is…err…thanks, I think. "This Regulation applies to all clinical trials conducted in the Union. It does not apply to non-interventional studies." >>as per Article 1 of Regulation EU/536/2014

* I'm using this as regulatory context in the hope that it will come into full effect in the near future. Otherwise, we would need to defer to the Clinical Trials Directive (Directive 2001/20/EC) and GCP Directive (2005/28/EC), but I'd rather this discussion be forward looking.