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PEER REVIEWED

Establishing the Link Between Trial Complexity and Coordinator Capacity

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The workforce of the clinical research enterprise continues to change and the demand for experienced professionals at the site, sponsor, and contract research organization (CRO) levels continues to increase. At a national level, there continues to be a lack of qualified professionals for both study coordinator and study monitors. This trend will continue as the appetite for clinical research at a site and sponsor level expands at an exponential rate. At the site level, meaningful assessment of workloads and understanding the capacity of teams are necessary to enhance job satisfaction, retain key talent, maintain high performance, and reduce turnover.

In an earlier article introducing this topic,{1} the authors described their experience and process in the development of a tool to assess the complexity of a clinical trial in a uniform way across any specialty and study type. Briefly, the first iteration of the tool was comprised of 21 unique elements, each with a possible score of 0–3 points, where 0 = least complex and 3 = most complex (see Figure 1).

Figure 1: Example of Original Complexity Tool

Complexity Tool				
Study Element	**No Effort**	**Minimal Effort (1 point)**	**Moderate Effort (2 points)**	**Maximum Effort (3 points)**
Active Scoring Elements				
PI expertise and experience with clinical research	N/A	Physician has been lead P.I. on several trials and has a clear understanding of a P.I.'s responsibilities	Physician has been Sub -I on a study(ies) and has enrolled and followed patients on a clinical trial	Physician has minimal research experience and/or requires an increased level of engagement
Study recruitment	N/A	Development of flyers or adding to LCD screens	Community outreach	Specialized recruitment efforts will be required
Target enrollment	0	<20	20 - 100	> 100
Inclusion/exclusion criteria	N/A	1-10 Inclusion/ exclusion criteria	11-20 inclusion/ exclusion criteria	> 21 Inclusion/ exclusion criteria
Informed consent process (initial)	No informed consent	1-10 pages	11-19 pages	> 20 pages
Screening procedures for eligibility (post consent)	0	1-5	6-10	≥ 10
Screening visit (length)	N/A	< 4 hours	4-8 hours	Over 8 hours
Randomization/baseline cycle 1 procedures	0	1-5	6-10	≥ 10
Baseline visit/ randomization (length)	N/A	< 4 hours	4-8 hours	Over 8 hours
Personnel required other than the research team, feasibility of the study	N/A	Involves only the research team,	Involves moderate number of different medical disciplines and staff	Involves high number of different medical disciplines and staff, requires more effort and coordination
Procedures needed after baseline/randomization to end of treatment (outside of procedure/drug)	0	1-10	11-20	≥ 21

For example, we included items scored on values such as recruitment strategies, principal investigator (PI) experience, number of screening procedures, number of visits, number of departments involved, frequency of monitoring, and activities at follow-up. An example would be how a score of 1 would be assigned if a study involved one department, but a study with more

than departments including the hospital would score a 3. The total possible score across all items is 63 points.

Additional elements of the complexity tool relate to the overall study design, team engagement, target accrual, consenting processes, length of study, monitoring elements, billing requirements, and if there are any associated ancillary studies.

From there, the research leadership team at the Mayo Clinic in Florida was able to develop a standard based upon natural breaks in the bell curve of the scores. The breaks indicated what would be considered a high, moderate, or low complexity trial design from a complexity standpoint for each clinical research unit.

Development of Version 2 of the Complexity Tool

Through its implementation, the research leadership team quickly identified a key area that could be improved in the Complexity Tool—the elements that were scored were done in such a way that all items were given equal weight. However, many items had a stronger impact than others on the complexity of a study. For example, the amount of data collection and requirements for reporting serious adverse events had a greater impact on coordinator effort than internal billing requirements or the length of a study subject's visit. Therefore, a review of the 21 elements was performed and those items that were felt to have a high impact on complexity of effort were weighted (see Figure 2).

Figure 2: Example of Weighted Complexity Tool

Study Element	No Effort (0 points)	Minimal Effort (1 point)	Moderate Effort (2 points)	Maximum Effort (3 points)	Weight
Study Scope/Overall Complexity					
PI expertise and experience with clinical research-number of years and levels of experience the PI has.	N/A	Principal Investigator (PI) was lead on several trials and has a clear understanding of a PI responsibilities	PI has been Sub -I on a study (ies) and has enrolled and followed patients on a clinical trial	PI has none or minimal research experience and/or requires an increased level of engagement	1.6
Study Recruitment-estimated effort needed or complexity in subject recruitment activities.	N/A	Development of flyers or adding to LCD screens	Community outreach-Outside physician referrals	Specialized recruitment efforts will be required-Radio or TV ads, talks in the community	1.2
Target accrual-number of subjects planned to meet the study enrollment criteria and receive study treatment. Captured from budget for Mayo Clinic Florida target (if applicable).	0	<20	20 - 100	> 100	1.6
Eligibility Criteria-number of key requirements for subjects to participate in a clinical study. Consists of both inclusion and exclusion criteria.	N/A	1-10 eligibility criteria	11-20 eligibility criteria	> 21 eligibility criteria	1.6
Informed consent process (initial)-number of pages for informed consent. Does not include addendums.	No informed consent	1-10 pages	11-19 pages	> 20 pages	1.3
Screening procedures for eligibility- The number of procedures that need to take place after subject signs informed consent form prior to administration of treatment. Note: One lab draw with 5 studies would count as 1 procedure. If the subject will need to go to separate labs, this would be counted separately.	0	1-5	6-10	> 10	1.4
Screening visit (length)-Length of visit(s) required to determine subject eligibility for accrual.	N/A	< 4 hours	4-8 hours	Over 8 hours	1.4
Randomization/ Baseline Cycle 1 Procedures-Study procedures before the randomization visit can even occur (e.g. internal required registration, sending an eligibility packet to the sponsor, etc.)	0	1-4	5-9	> 9	1.4
Randomization/ Baseline Cycle 1 Length-time it takes for subject to complete visit where they receive their first study treatment.	N/A	< 4 hours	4-8 hours	Over 8 hours	1.4
Additional Personnel Needed-Personnel required outside of the core research team required to complete study procedures. Core research team is generally defined as the PI, CRC and Clinical Research Assistant.	N/A	Involves only the research team-PI, Study Coordinator and Clinical Research Assistant	Involves moderate number of different medical disciplines and staff-may include infusion unit, clinic nurses, genetic counselor etc./approx. 3 add'l teams	Involves high number of different medical disciplines and staff, requires more effort and coordination-may include involvement of hospital staff, overnight staff etc./approx. 4 add'l teams	1.4
Procedures needed after Baseline/ Randomization to End of Treatment (outside of treatment)-The average number of study procedures that occur at study visits during active treatment until the subject completes trial treatment. Note: each set of labs, EKGs etc. all count separately.	0	1-10	11-20	> 21	1.6

Scores were weighted by a multiplier ranging from 1.2 to 1.7 across all 21 items. Less complex or less time-consuming items were multiplied by 1.2 (e.g., type of study recruitment). The most complex and time-consuming items were multiplied by 1.7 (e.g., adverse event reporting).

From these weighted scores, the total possible score changed from 63 to a balanced and more relatable score of 100 points. This also allowed for a more intuitive breakdown of the high-, moderate-, and low-complexity categories across a 100-point spread.

Studies that were open to enrollment and new studies going forward, were assessed with the new weighted complexity score. This model has been implemented and sustained for the last two years.

Correlating Trial Complexity with Coordinator Capacity

Once a final version of the Complexity Tool was in place, the research leadership team in Mayo Clinic Florida aimed to use the complexity score as a baseline determinant of a clinical research coordinator's (CRC's) capacity. Various disease teams were reviewed; leadership chose examples of teams that appeared understaffed, adequately staffed, and overstaffed, to see if the "gut feeling" from the management team held true when the new scoring was applied.

As a small test of change, the leadership team selected three teams (disease pods) within the Cancer Clinical Research Office (CCRO) with their initial assumption that one disease pod was understaffed (gastrointestinal [GI] cancer), one was adequately staffed (breast cancer), and a third had capacity to take additional studies (leukemia). These three disease pods' scores were reviewed and a composite score per group was determined (see Figure 3). The score was then divided by the allocated CRC full-time employees (FTEs). After comparing the scores for the three sample disease pods, the leadership team identified a predictive score of 350 points as a potential target capacity score for a CRC.

Figure 3: Scores by Disease Pod within the CCRO			
	Breast Cancer Team*	GI Cancer Team**	Leukemia Team***
Total Team Score	1,197	938	789
FTE in the Team	3	2	3
Score per FTE	399	469	263
*Disease pod was adequately staffed for the workload **Disease pod was slightly understaffed ***Disease pod was overstaffed or has capacity to take on additional studies			

From there, the remaining disease pods within the CCRO were scored. The leadership team then completed a stakeholder analysis and reviewed metrics with the CRCs, data coordinators, and PIs, to understand their level of understanding of the workload and what they felt was an ideal state or workload. Through these discussions, the team was able to finalize that the ideal workload for a CRC within the CCRO was a score of 375–400 points. Once a target workload score per coordinator was established, research leadership further engaged their PI community on campus to review the needs and existing resources of each disease pod.

Over the last three years, clinical trial activity on the Mayo Clinic Florida campus has tripled in volume and complexity. With finite space to add new staff, assessing capacity of the existing team, reallocating resources, and having meaningful discussions of closing non-recruiting studies have received increased levels of attention.

Through the use of the Complexity Tool and the creation of a “CRC Standard,” a maximum score per disease pod was able to be determined based upon their allotted FTEs. For example, if one assumes the maximum complexity score per CRC is 400, and GI cancer has two FTEs of coordinator support, the maximum score would be 800. When investigators were interested in opening new trials, the current pod score was reviewed to determine if there was capacity within the team to take on another study.

With the Complexity Tool, studies ranged generally from a score of 10–100. If there was adequate capacity (e.g., disease pod score of 600), the study was able to open without further review. If there was limited capacity available (e.g., disease pod score of 790), research leadership, in partnership with clinical department practice chairs, would review the disease pod's portfolio of existing and in-development studies to determine if there were studies that were underperforming that could be closed, or if there were competing studies that would prohibit the proposed study. If no such situations occurred, the amount of additional required FTEs would be reviewed.

Before posting for a new hire, research leadership would review other disease pods that had capacity to determine if coverage could be attained within the clinical research unit. The research leadership team is currently in the process of implementing a model whereby teams that are at or near capacity, but that cannot financially support an additional full FTE, will be able to share a "floater CRC" resource with other teams. As portfolios grow, the existing floater CRC would become dedicated to a specific team when the need arises.

Linking Capacity to Budgeted Effort

The next step was to determine if the weighted complexity score could serve as a predictive measure of how much coordinator effort should be budgeted for a clinical trial. Research leadership retrospectively reviewed a sample of studies within the CCRO to document how much effort was originally indicated by the coordinator to complete study tasks versus the complexity score calculated (using the 100-point weighted scale).

Complexity scores for this subset of studies ranged from 25 to 81 and were categorized into three ranges: 25–45, 46–65, and 66–85. The average percentage of effort per a subject (without taking into account the number of visits) was 11%, 28%, and 40%, respectively (see Figure 4). We did not evaluate above 85 points for the retrospective review, as no studies had a score that high to include.

Figure 4: Predictive Measure		
Complexity Score (out of 100 possible points)	Complexity Level	Average % Effort for CRC
25–45 points	Low	11%
46–65 points	Moderate	28%
66–85 points	High	40%

When reviewing the amount of effort spent by the coordinator on the trials, rule sets were established based upon the complexity score. For example, in the CCRO, every study that had a complexity score greater than 55 utilized a minimum of 35% of coordinator time, with the majority of these studies being Phase I. By understanding the minimum amount of effort required for a trial, based upon the complexity score, we are now in a better position to develop more accurate study budgets and have precedent to draw upon to assist in the negotiation of per-patient amounts with trial sponsors.

Current State

Through this review, rule sets based upon the complexity score are now being established that will allow for a more solid foundation upon which the assumption of CRC time could be based. The leadership team is in the process of creating a mechanism through which feasibility could easily be determined based upon negotiability of a proposed budget. It will also allow for proactive conversations with the PI on studies that may require financial supplementation in order to support FTEs to open the study, and will create a standard that could be expanded to other roles, such as data coordinators.

Reference

1. Richie A, Gamble D, Tavlarides A, Griffin C. 2019. Trial complexity and coordinator capacity: the development of a complexity tool. *Clin Res* 33(5), 17–23. https://acrpnet.org/2019/05/14/trial-complexity-and-coordinator-capacity-the-development-of-a-complexity-tool/

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PEER REVIEWED

Interventional or Non-Interventional? Analyzing the Differences Between Clinical Studies Using Medicines in the European Union

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Clinical Trial Regulation (EU) No. 536/2014 (REG 536/2014),{1} signed off on April 16, 2014, aims to simplify current rules, streamline trial application procedures, improve transparency, and harmonize clinical trial practice throughout all the Member States of the European Union (EU), in alignment with the tenets of the International Council for Harmonization (ICH) Good Clinical Practice (GCP) guideline.{2} This regulation has an extensive scope within clinical trials, covering authorization procedures, ethical considerations, implementation, operations, and disclosure, among other topics.

However, REG 536/2014 is not yet in force; currently, researchers rely on the Clinical Trial Directive (DIR 2001/20/EC),{3} which merely provides the definitions and requirements Member States must adopt into their own local legislation. It is important to note that non-interventional studies are out of the scope of both the current DIR 2001/20/EC and the upcoming

REG 536/2014. As a result, there is significant variability in the classification of non-interventional studies across EU Member States with consequent impacts on their planning and execution on a multinational scale.

This paper aims to overview each type of clinical study referred to within the upcoming REG 536/2014 and analyze their impact upon the implementation of this Regulation, as well as the expected framework for non-interventional studies. For improved navigation, please refer to Table 1 for a list of abbreviations and acronyms used in this paper or otherwise tied to this topic.

Table 1: Useful Abbreviations and Acronyms

DIR 2001/20/EC	Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations, and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use
EC	Ethics Committee
EMA	European Medicines Agency
EU	European Union
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database
GCP	Good Clinical Practice
GVP	Good Pharmacovigilance Practices
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product
PASS	Post-authorization safety study
PRO	Patient-reported outcome
REG 536/2014	Clinical Trial Regulation (EU) No. 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC

Clinical Studies

Article 2 of REG 536/2014 defines a "clinical study" as 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.

This section further defines clinical studies as either "clinical trials," "low-intervention clinical trials," or "non-interventional studies." Table 2 compares each clinical study type in terms of study objectives, methods, population, and regulatory/ethical requirements, in alignment with REG 536/2014.

Table 2: Comparison of Study Types

	Clinical trial	**Low-intervention trial**	**Non-interventional study[a]**
Objectives	**Pre-marketing**: pharmacology, safety, and efficacy information for MAA. **Post-marketing**: to refine understanding of benefit/risk relationship under therapeutic use conditions and in accordance with the MAA.	**Pre-marketing**: pharmacology, safety and efficacy information for MAA, but IMP use is evidence-based and supported by published evidence. **Post-marketing**: to refine understanding of benefit/risk relationship under therapeutic use conditions and in accordance with the MAA.	**Pre-marketing**: not applicable. **Post-marketing**: to refine understanding of benefit/risk relationship under therapeutic use conditions, in accordance with the MAA and following normal clinical practice.{9}

Methods	Usually prospective, although there may be exceptions (case study 2 in Table 4). Treatments and procedures defined in the protocol. Monitoring and operations according to the ICH GCP guideline.	Usually prospective, although there may be exceptions (case study 2 in Table 4). Treatments and procedures defined in the protocol. Less stringent operations compared to other clinical trials.	Can be retrospective, cross-sectional, or prospective. Treatment and procedures follow clinical practice and cannot be imposed by the protocol.{3} Treatment prescription independent from study inclusion.{3} No harmonized European guidance or regulation for operational activities.
Population	Sample size depends on the study objectives. Usually stricter eligibility criteria.	Sample size depends on the study objectives. Sample sizes may be higher and eligibility criteria may be less strict than early-phase clinical trials.	Large sample sizes and heterogenous populations to reflect real-world conditions. Exclusion criteria usually compliant with the MAA.
Ethical requirements	EC favorable opinion. ICF mandatory.	Same as other clinical trials.	EC favorable opinion. ICF typically mandatory (may be waived under specific conditions).
Regulatory requirements	Competent authority(ies) authorization. Registration and disclosure in EudraCT. Country-specific regulations may require additional steps.	Same as other clinical trials.	Imposed PASSs: approval from PRAC (or local authority, if conducted in only one Member State).{9} PASSs: registration in the EU PAS.{9} Country-specific regulations may require additional steps.

			Local authority consulting may be advisable to confirm non-interventional status.

[a] Non-interventional studies are not scoped in the REG 536/2014. This table presents guidance and requirements from other regulatory sources applicable to the European Union.

References: Directive 2001/20/EC,{3} Guideline on good pharmacovigilance practices Module VIII.{9}

Abbreviations: EC Ethics committee; EU PAS European Union Electronic Register of Post-Authorization Studies; EudraCT European Clinical Trials Database; GCP Good Clinical Practice, ICF Informed consent form; ICH International Council for Harmonization; IMP Investigational medicinal product; MAA Marketing authorization application; PASS Post-authorization safety study; PRAC Pharmacovigilance Risk Assessment Committee.

Clinical Trials

Article 2 of the REG 536/2014 defines a “clinical trial” as a clinical study whose treatment strategies, diagnostic assessments, and clinical monitoring procedures are determined and scheduled in advance by a clinical trial protocol, and do not fall within normal clinical practice.

Clinical trials are required before an investigational medicinal product (IMP) is authorized to be commercialized for the intended therapeutic indication(s). These trials collect pharmacological, safety, and efficacy information from human participants needed for marketing authorization.{4} Clinical trials are also performed after marketing authorization is granted, to refine understanding of the benefit/risk relationship under real-world therapeutic use conditions.{4}

All clinical trials performed in the EU should receive authorization from the competent authority(ies) and be registered in the European Clinical Trials Database (EudraCT) prior to starting.{1,5} Country-specific regulations may require additional regulatory steps (e.g., approval of local data protection authorities or registration in local clinical trial databases). A favorable opinion from all applicable ethics committees (ECs) and an approved informed consent form are required.{1,6}

Low-Intervention Clinical Trials

The concept of “low-intervention clinical trial” is first introduced in the upcoming REG 536/2014 and is not part of the DIR 2001/20/EC. These trials use authorized drugs (excluding placebos) in accordance with the marketing authorization, or non-authorized drugs, if their use is evidence-based and supported by the published scientific evidence. These trials should not pose more than a minimal additional safety risk or burden to participants compared to normal clinical practice.{7}

As in all clinical trials, the assessment and treatment procedures of low-intervention clinical trials are to be determined by the protocol. However, less stringent requirements may be applicable. Specific conduct requirements should be based on a risk evaluation assessment to be performed for each trial.{7} Sponsors must be familiar with REG 536/2014, the European Commission guidance document describing Risk Proportionate Approaches in Clinical Trials, and applicable legislation of the target EU Member States to perform an appropriate risk evaluation and propose adequate conduct approaches. On the other hand, regulatory and ethical submission and authorization requirements for low-intervention clinical trials are the same as for other clinical trials.{1}

One potential concern regarding the introduction of the low-intervention trial concept is the lack of EU-consistent regulatory definition for “minimal additional safety risk or burden” in the upcoming REG 536/2014. As such, upon implementation of the new Regulation, there may be difficulties in defining a study that falls upon the borderline between a non-interventional and low-intervention definition. This can result in a single study being considered as non-interventional in some Member States and as a clinical trial in others. Due to this situation, it can be difficult for sponsors to meet the study application requirements and compliance expectations.

To avoid such inconsistencies, the REG 536/2014 aims to provide a clear and harmonized definition for low-intervention clinical trials. To further reduce ambiguity, in June 2019, the European Commission issued the REG 536/2014 Draft Questions & Answers document, which has been frequently updated since that time (currently Version 2.3, dated November 2019, at time of writing).{8} Annex II of this document includes a decision tree aiming to establish whether a study is a clinical trial, a non-interventional study, or a low-intervention clinical trial, following some key aspects (i.e., whether the drug is an IMP, what effects is the study looking for and their purpose) (see Table 3).

Table 3: Decision Tree for Determining Study Type (Transcribed from Regulation [EU] No 536/2014 Draft Questions & Answers Version 2.3)

	A	**B**	**C**	**D**	**E**	**F**
A clinical trial of a medicinal product?					**A non-interventional study?**	**A low-intervention clinical trial?**
Is a medicinal product administered before or during the start of the clinical trial?	Is it a medicinal product?[i]	Is it not a medicinal product?	What effects of the medicine are you looking for?	Why are you looking for those effects?	How are you looking for these effects?	Is the product authorized in any EU Member State?
If a medicinal product is administered before the start of the clinical trial, and it falls under current practice, please go to column E.	If you answer no to <u>all</u> the questions in column A, the activity is not a clinical trial on a medicinal product.	If you answer yes to the question below in column B, the activity is not a clinical trial on a medicinal product.	If you answer no to <u>all</u> the questions in column C, the activity is not a clinical trial under the scope of Regulation EU No 536/2014.	If you answer no to <u>all</u> the questions in column D, the activity is not a clinical trial under the scope of Regulation EU No 536/2014.		

If a medicinal product is administered before the start of the clinical trial and it falls not under current practice, column E is excluded. If a medicinal product is administered after the start of the clinical trial, please go to column A.	If you answer yes to any of the questions below, go to column B.	If you answer no to this question below, go to column C.	If you answer yes to <u>any</u> of the questions below, go to column D.	If you answer yes to <u>any</u> of the questions below, go to column E.		
	A.1. Is it a substance[ii] or combination of substances presented as having properties for treating or preventing disease in human beings? A.2. Does the substance function as a medicine? (i.e., can it be administered to human beings either with a view	B.1. Are you only administering any of the following substances? • Human whole blood[iii]; • Human blood cells; • Human plasma; • A food product[iv] (including dietary supplements)	C.1. To discover or verify/compare its clinical effects? C.2. To discover or verify/compare its pharmacological effects? (e.g., pharmacodynamics) C.3. To identify or verify/compare its adverse reactions? C.4. To study or verify/compare its pharmacokinetics? (e.g., absorption, distribution,	D.1. To ascertain or verify/compare the efficacy[vi] of the medicine? D.2. To ascertain or verify/compare the safety of the medicine?		

	to restoring, correcting, or modifying physiological functions by exerting a pharmacological, immunological, or metabolic action; or with a view to making a medical diagnosis; or is it otherwise administered for a medicinal purpose?) A.3. Is it an active substance in a pharmaceutical form?	not presented as a medicine; • A cosmetic product [v]; • A medical device	metabolism, or excretion)			

[i] Cf. Article 1(2) of Directive 2001/83/EC, as amended.

[ii] Substance is any matter irrespective of origin e.g. human, animal, vegetable, or chemical that is being administered to a human being.

[iii] This does not include derivatives of human whole blood, human blood cells, and human plasma that involve a manufacturing process.

[iv] Any ingested product which is not a medicine is regarded as a food. A food is unlikely to be classified as a medicine unless it contains one or more ingredients generally regarded as medicinal and indicative of a medicinal purpose.

[v] The Cosmetic Directive 76/768/EC, as amended harmonizes the requirements for cosmetics in the European Community. A "cosmetic product" means any substance or preparation intended for placing in contact with the various external parts of the human body (epidermis, hair system, nails, lips, and external genital organs) or with the teeth and mucous membranes of the oral cavity with the view exclusively or principally to cleaning them, perfuming them, or protecting them in order to keep them in good condition, change their appearance, or correct body odors.

[vi] Efficacy is the concept of demonstrating scientifically whether and to what extent a medicine is capable of diagnosing, preventing, or treating a disease and derives from EU pharmaceutical legislation.

References: REG 536/2014 Q&A Version 2.3 (transcribed from Annex II).{8}

Abbreviations: Q&A Questions & answers; REG Regulation.

However, these efforts toward harmonization may have an impact on the current standard practice. As an example, most Member States will currently allow post-authorization safety studies (PASSs; see next section for definition) utilizing patient-reported outcome (PRO) questionnaires to be run as non-interventional studies.{9} Meanwhile, Article 2 of the REG 536/2014 provides that low-intervention clinical trials may include "additional diagnostic or monitoring procedures [that] do not pose more than minimal additional risk or burden to the safety of the subjects compared to normal clinical practice in any Member State concerned." Under this definition, it is possible that, upon implementation of the new Regulation, non-interventional studies using PROs not normally used in routine practice may be classified as low-intervention clinical trials, with regulatory requirements equivalent to a clinical trial. The impact of this attempt at harmonization remains to be seen.

Being only part of the upcoming REG 536/2014, the designation of low-intervention clinical trial is not yet in force in any EU Member State, with the exception of Spain, which adopted REG 536/2014 into local law in December 2015 (Real Decreto 1090/2015).{10} In fact, some national authorities in some Member States have moved ahead with revisions to local regulations that deviate from the low-intervention clinical trial definition provided in the REG 536/2014. An example is the legislation released in France in 2016 (Code de la santé publique – Article L1121-1),{11} following publication of the final EU Regulation text. The French law reorganized study classification into category 1, 2, and 3 research. While category 3 research remained harmonized with the definition of a non-interventional study provided in the current DIR 2001/20/EC, category 2 research is interventional research where the drug product is not the object of the research and where the intervention (i.e., a blood sample) poses minimal risk to patients. Any low-intervention clinical trial involving a drug product would continue to fall under category 1

research, and is subject to full clinical trial requirements according to French regulations. Further modification of the law therefore appears necessary upon REG 536/2014 coming into force.

Non-Interventional Studies

Article 2 of DIR 2001/20/EC defines a “non-interventional study” as a study where the medical product(s) is (are) prescribed independent to inclusion of the participant in the study and as part of a therapeutic strategy, including diagnostic and monitoring procedures, which is not decided in advance by a study protocol but is applied according to the current clinical practice. As such, these studies seek to understand the use of a marketed product in real-world conditions, including risk/benefit, healthcare resource utilization, and patient/caregiver satisfaction, as examples.

Another example is the non-interventional PASS, a study carried out to obtain further information on a drug’s safety, or to measure the effectiveness of risk-management measures{9} (note: PASSs may also be designed as interventional studies, which require following the applicable clinical trials regulations).

In non-interventional studies, clinical procedures and assessments must follow normal clinical practice, as opposed to clinical trials, which follow the protocol. However, the definition of “normal clinical practice” may be subjective and prone to disagreement. For clarity and harmonization, the European Medicines Agency (EMA) Guideline on Good Pharmacovigilance Practices (GVP) Module VIII states that in non-interventional studies, “interviews, questionnaires, blood samples and participant follow-up may be performed as part of normal clinical practice.” However, the application of such assessments should not be conducted in a way that is considered significantly different from clinical practice.{9}

Although defined in DIR 2001/20/EC, non-interventional studies are outside its scope. Due to the lack of harmonized regulation, some studies designed to be non-interventional may be considered clinical trials by EU authorities. The two blinded studies described in Table 4 were considered clinical trials in the EU for planning on collection of data to support the marketing authorization application of experimental IMPs, despite no IMP being given and normal clinical practice being kept during the study period. Sponsors are thus advised to consult with authorities when planning studies under these conditions and/or whenever the objectives or design may raise questions.

Table 4: Examples of Decisions and Rationale for Classifying Two Studies*

#	Study description	Authority decision and rationale
1	• Long-term safety follow-up of participants with Disease A, under normal clinical practice. • Participants previously exposed to experimental Drug A in a clinical trial for the management of Disease A. • Drug A had been stopped prior to study initiation.	**Clinical trial** • Drug A was not authorized for Disease A at the time the long-term safety follow-up study was initiated. • Population was exposed to an investigational product under clinical trial conditions, as opposed to a real-world exposure. • Data collected in consequence of previous experimental exposure to Drug A and to support the marketing authorization of Drug A. • Rationale for this decision was subsequently supported by the REG 536/2014 Draft Q&A Version 2 document (question 1.15).{8}
2	• Use of previously collected blood samples in participants with Disease B to determine potential genetic markers. • Participants previously exposed to experimental Drug B in a clinical trial for the management of Disease B.	**Clinical trial** • Population was exposed to an investigational product under clinical trial conditions, as opposed to a real-world exposure. • Drug B did not have marketing authorization.

	• Blood samples aimed at correlating Disease B biomarkers with potential efficacy of Drug B. • Drug B had been stopped prior to study initiation.	• Despite no direct patient interaction, blood samples would be tested and results analyzed to support the marketing authorization of Drug B.

*The examples in this table are of real clinical studies that have been blinded for confidentiality purposes. These were considered clinical trials by EU authorities, despite not involving exposure to an investigational product during the study period.

References: REG 536/2014 Q&A Version 2.{8}

Abbreviations: EU European Union; Q&A Questions & answers; REG Regulation.

Due to the lack of harmonized EU guidance or regulation regarding non-interventional studies' operations and monitoring activities, sponsors and investigators must ensure the safety of study participants and the collection of high-quality data by following an appropriate study plan. Some EU regulations and guidelines should be followed for this purpose, including, but not limited to:

- Regulation 2016/679 on personal data protection.{12}
- Directive 2010/84/EU on pharmacovigilance and safety reporting (Article 107).{13}
- Directive 2001/83/EC on labelling requirements.{14}
- EMA GVP Module VIII, specific to PASS.{9}
- European Centers for Pharmacoepidemiology and Pharmacovigilance considerations on the definition of non-interventional trials.{15}
- Guidelines for good pharmacoepidemiology practice.{16}
- Applicable legislation and guidance issued by EU Member States.

There is no centralized submission procedure for non-interventional studies with the exception of non-interventional PASSs, imposed as an obligation by an EU competent authority.{9} Because non-interventional studies do not have harmonized legislation, some Member States require submissions to regulatory authorities, while others do not. It is therefore important that sponsors are familiar with the regulatory framework of target EU Member States, and that they consult with local competent authorities and ethics committees (ECs) when justified.

Non-interventional studies generally do not require registration in an EU database, with the exception of non-interventional PASSs, which must be registered in the EU Electronic Register of Post-Authorization Studies.{9} Nevertheless, some Member States may require registration in local databases, so sponsors should look to confirm this possibility.

As for ethical requirements, a favorable opinion of the central or local ECs (depending on local regulations) is required for all non-interventional studies, with the exception of Denmark. Informed consent is typically required.

After implementation of the upcoming REG 536/2014, the aforementioned variability in local requirements across the EU is expected to continue as these studies do not enter the scope of this Regulation, being only defined as a “clinical study other than a clinical trial” (Article 2). This will not be problematic if all EU Member States are willing or able to update their local legislation to define non-interventional studies consistently across the EU. However, it is not clear that this will be the case.

The lack of a single, explicit regulatory definition for these studies can result in different interpretations from Member States when presented with the same study, with regulatory and operational consequences. If one Member State considers a study interventional, it will need to

follow all low-intervention clinical trial–specific requirements defined in REG 536/2014, substantially different from what is expected from a non-interventional study. As addressed earlier, this can be of special concern if a study falls upon the borderline between non-interventional and low-intervention definitions.

The European Authorities are conscious of the challenges that lie ahead. Within the currently available guidance on interpretation of the REG 536/2014{8} there are currently seven questions in the first section of the Q&A document related to the definitions of a low-intervention clinical trial and/or a non-interventional study. In addition, the frequency of updates being applied to this guidance document (four separate version updates between June and November 2019) indicates the importance of clarifying points such as these.

Based on this history, there can be hope that the European Commission will continue to provide clarifying guidance that sponsors and investigators can use to influence individual ECs and competent authorities within EU Member States if they face disharmonized opinions. However, in order to effectively plan a low-intervention clinical trial, it will remain important that all sponsor-related stakeholders are aware of the potential pitfalls that exist in relation to these definitions.

Conclusion

Upon implementation of REG 536/2014 in the EU, three different clinical study definitions are to be considered: clinical trial, low-intervention clinical trial, and non-interventional study.

Non-interventional studies are outside the scope of this Regulation, similar to the current DIR 2001/20/EC. With the lack of a harmonized EU regulatory definition for these studies, after the implementation of the new regulation it is expected that the variability in the classification of

non-interventional studies across EU Member States will continue. In addition, the implementation of a low-intervention clinical definition may lead to studies currently considered non-interventional to be considered clinical trials in the future, with operational and regulatory consequences.

Sponsors must be prepared not only for the upcoming EU Regulation, but also for how the Member States will adapt their own legislation after its implementation, as this will have potential impact in the clinical development of their products.

Disclaimer

The opinions expressed in this paper are the authors' own and not necessarily shared by their employer.

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HOME STUDY

Research Studies and Studying Research: Designing a Better Tomorrow

Article 1—Establishing the Link Between Trial Complexity and Coordinator Capacity

LEARNING OBJECTIVE

After reading this article, the participant will be able to describe the development and application of a weighted complexity tool for determining trial complexity and coordinator capacity.

DISCLOSURE

Alexa Richie, DHSc; Dale Gamble, MHSc; Andrea Tavlarides, PhD; Kate Strok, CCRC, CCRA;
Carol Griffin: *Nothing to disclose*

1. Which of the following is cited as a meaningful assessment of workloads and research capacity at sites?

A. Improving public perceptions of trials
B. Simplifying budget negotiation processes
C. Reducing turnover rates for site staff
D. Avoiding legal actions from study sponsors

2. The original Complexity Tool described by the authors included items scored on which of the following study elements?

1. Study recruitment
2. Disease severity
3. Inclusion/exclusion criteria
4. Personnel requirements

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

3. What was the total possible complexity score from the original Complexity Tool?

A. 52 points
B. 63 points
C. 74 points
D. 85 points

4. **Why was a major scoring change made during the development of the second version of the Complexity Tool?**

A. Sites that tested the original version found it too simplistic.
B. Sponsors warned they would not support sites using the tool.
C. Common errors in scoring procedures caused staffing overloads.
D. Some elements had stronger impacts than others on complexity.

5. What is the updated Complexity Tool's maximum possible score?

A. 75 points
B. 100 points
C. 125 points
D. 150 points

6. In testing the Weighted Complexity Tool, which of the following characteristics of the disease teams were reviewed?

A. Understaffed, adequately staff, overstaffed
B. Underbudgeted, adequately budgeted, overbudgeted
C. Underqualified, adequately qualified, overqualified
D. Undertested, adequately tested, overtested

7. In evaluating coordinator capacity, what was found to be the ideal range for a full-time equivalent (FTE) study coordinator workload score?

A. 225 to 250 points
B. 300 to 325 points
C. 375 to 400 points
D. 450 to 475 points

8. How do principal investigators use the "disease pod score" when opening new trials?

A. To assign newer coordinators to gradually more challenging studies over time.
B. To compare the workload scores for their teams to teams at other institutions.
C. To negotiate for more sponsor support during certain highly complex studies.
D. To determine if there is capacity within their team to take on another study.

9. Which of the following is an option the authors mention as being used to deal with research teams that are overburdened but cannot take on another full FTE coordinator?

A. Dropping the newest study(ies) in progress until the staffing is adequate again.
B. Sharing a floater study coordinator resource with other disease pod teams.
C. Temporarily taking on only the least complicated studies possible.
D. Asking study sponsors to directly fund the hiring of extra site staff.

10. Which of the following are cited as advantages of using complexity scores to understand the minimum efforts required for trials?

A. Negotiating with sponsors on per-patient amounts and developing study budgets.
B. Determining salary awards for high recruitment levels and eliminating poorly performing staff.
C. Asking sponsors to minimize protocol amendments and setting inclusion/exclusion criteria.
D. Deciding on new indications to pursue studies in and gauging patient follow-up efforts.

Article 2—Interventional or Non-Interventional? Analyzing the Differences Between Clinical Studies Using Medicines in the European Union

LEARNING OBJECTIVE

After reading this article, the participant will be able to describe differences between Clinical Trial Regulation (EU) No. 536/2014 and the Clinical Trial Directive 2001/20/EC, and implications for determining if specific trials are to be defined as interventional or non-interventional in the European Union.

DISCLOSURE

Tiago Silva, MSc; Alexandra Parnell, MSc; Christopher Bamford, PhD; Catherine Paulen, PharmD; Simona Francisconi, MSc; Jaclyn Bosco, PhD, MPH; Louise Parmenter, PhD, MSc: *Nothing to disclose*

11. With what other document is the Clinical Trial Regulation (EU) No. 536/2014 in alignment?

A. Clinical Trial Directive 2001/20/EC
B. The Belmont Report
C. ICH Good Clinical Practice guideline
D. *Code of Federal Regulations*

12. The authors specify which of the following as being out of scope of both REG 536/2014 and DIR 2001/20/EC?

A. Randomized, controlled trials
B. Basket trials
C. Crossover trials
D. Non-interventional trials

13. REG 536/2014 defines clinical studies in which of the following categories?

1. Clinical trials
2. Low-intervention trials
3. High-intervention trials
4. Non-interventional studies

A. 1, 2, and 3 only
B. 1, 2, and 4 only
C. 1, 3, and 4 only
D. 2, 3, and 4 only

14. All clinical trials performed in the EU should be registered in which of the following?

A. ClinicalTrials.gov
B. EudraCT
C. European Commission
D. ICH

15. Which of the following is a distinguishing characteristic of low-intervention clinical trials?

A. May involve drugs already on the market.
B. Must pose more than a minimal safety risk.
C. Compare only placeboes against each other.
D. They are only covered in DIR 2001/20/EC.

16. In which document can a decision tree for determining study types be found?

A. *Code of Federal Regulations* 21 CFR Part 312
B. DIR 2001/20/EC Supplementary Materials
C. REG 536/2014 Draft Questions & Answers
D. ICH Good Clinical Practice guideline

17. Which of the following is cited as an example of a non-interventional study allowed by most EU Member States?

A. A preclinical study examining patient preferences in medical device designs.
B. A Phase I study focused on maximum safe dosing levels for a repurposed drug.
C. An investigator-initiated study comparing similar over-the-counter therapies head to head.
D. A post-authorization safety study using patient-reported outcome questionnaires.

18. A non-interventional study seeks to understand the use of a marketed product under what conditions?

A. Non-biased
B. Placebo-controlled
C. Real-world
D. Low-stress

19. For what purpose are guidelines for good pharmacoepidemiology practice cited among the EU regulations and guidelines to be factored into preparations for non-interventional studies' operations and monitoring activities?

A. Following study plans for ensuring study participants' safety and collecting high-quality data.
B. Negotiating fair and balanced study budgets and publication timetables with study sponsors.
C. Hiring specialist study coordinators for handling complex protocol-related tasks.
D. Identifying low-intervention vs. non-interventional studies in a site's study portfolio.

20. Which of the following is true regarding EU Member States' approaches to non-interventional studies?

A. Legislation for such studies is harmonized across all Member States.
B. Legislation for such studies is not harmonized across the Member States.
C. Legislation for such studies is barred from being considered in Member States.
D. Legislation for such studies has caused some Member States to cease conducting them.