Discussion on stakeholder priorities to advise ACT EU Steering Group

MSP AG meeting 27 September 2024

Presented by Ana Zanoletty and Laura Pioppo

Introduction

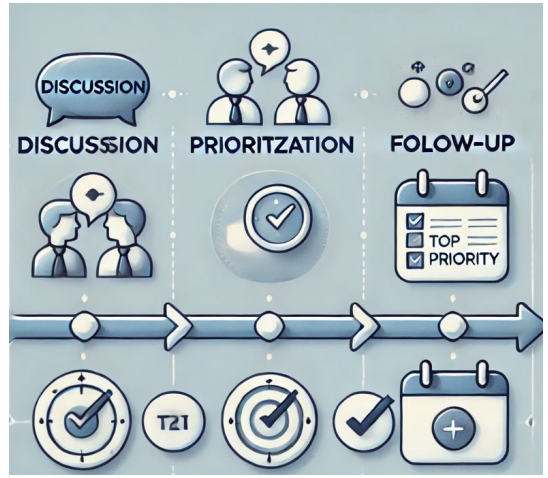
- Issues raised during the 4 July meeting
- Summarised by category
- To be prioritised

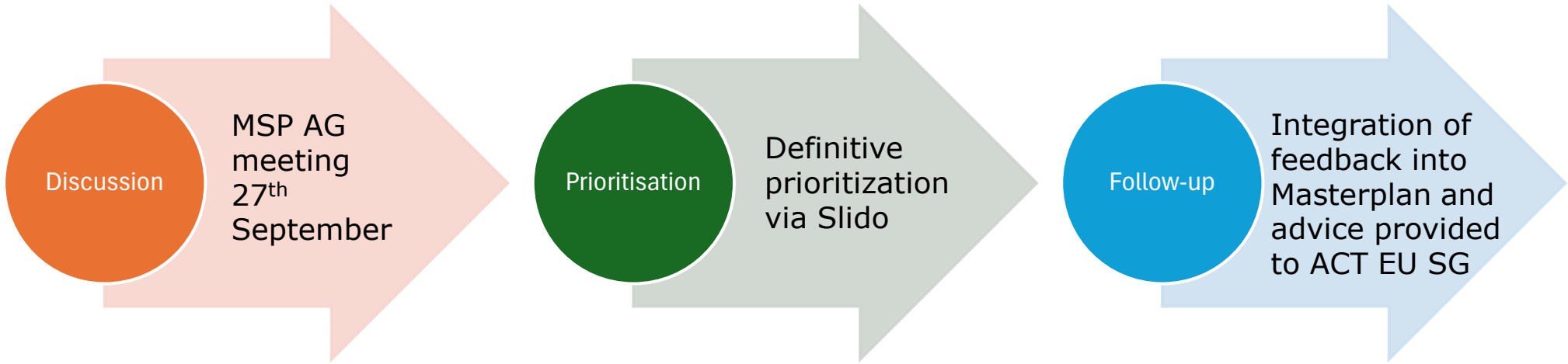
Issues and solutions discussed	Proposed summarized issue for voting/prioritising	Potential solutions menti
Large number of RFIs arising following assessment of Part 1 and especially of Part 2 Perception that some NCAs may be refusing some trials in order to meet timelines or that RFIs are compilations of individual comments rather than a consolidated set of key issues focused on priorities Sponsors limit the number of MSs included in the initial application in order to reduce the number of Part 2 questions in particular Perception that MS may respond negatively or with questions of limited value in order to keep timelines Reliance on Part 1 assessment bythe Reporting Member State (RMS), for both part 1 and part 2 review by MSs remains limited	CTR implementation faces issues with inconsistent RFI handling, uncoordinated processes causing delays, and varied national requirements. This leads to fewer applications by sponsors and highlights the need for unified standards to streamline the process.	Reliance on RMS assessment for Focus on issues that are of signifi the protection of clinical trials par Consistently raising RFIs that can Establish a mechanism for MSs ar responses where these have bee some degree of anonymization if approach, ensuring complete goo Develop some points to consider basis.
No triage of RFI is leading to inconsistent challenges for the Sponsor. Inconsistent timelines for approval processes i.e. early approval of Part II in anticipation of Part I is not advantages		Empowerment of RMS to group a prevent contradictory RFI, align with Ethics Committees
Approval with conditions, diverse and multiple RFIs, use of NSM (ICF), Part I/Part II interplay, non reliance on previous assessment		Need to streamline the process(es) and reduce the current lack of predictability, by strengthening the role of the RMS, allowing consistent use of currently existing as well as new efficiencies / flexibilities, and applying a risk-proportionate approach for review.
Role of RMS, RFIs, longer timelines, pressure on sponsors		
Lack of transparency in the EC's involvement in the review of PART I with some countries conducting joint reviews leading to duplicate questions or difficulty to address conflicting questions/ Linked to solution above – empower RMS to group and triage RFI Alignment with EC needed		Linked to solution above – empower RMS to group and triage RFI Ensure processes for alignment in Ethics Committees requirements for part II is in place
Local demands are still made for part II documents and there is no scope for a sponsor to refuse or escalate to drive alignment as per regulation.		
Site details, progress reports, patient cards, PoP (and multiple payments), investigator team details (inc. names)		Need to agree on common requirements limiting / eliminating the current national flexibility for requirements beyond CTR.
Inability to submit parallel SMs is a challenge for feasibility of master protocol in EU with several IMPs (regular IB, IMPD and protocol amendments).	Modify rules for submission of amendments should be implemented in CTIS, particularly important for CCT. Establish communications channels between sponsors and member states.	Enable parallel substantial modifications. Run pilots with sponsors to understand applicability to pivotal trials
No parallel SMs, No NSM for (all) minor changes, no flexible communication with reviewers, need CTIS workarounds for trials, IMPD-Q process. A truly holistic and future-ready approach to improving the EU regulatory framework for clinical research is needed. Further flexibilities should be applied, while CTIS also requires improvement, including allocation of new capabilities.		

Category	Subcategories	Issues & solutions discussed	Additional comments originating from the 4 July meeting
CTR implementation	National requirements	Site details, progress reports, patient cards, PoP (and multiple payments), investigator team details (inc. names) Need to agree on common requirements limiting / eliminating the current national flexibility for	Connect stakeholders to CTR Collaborate to discuss challenges and agree on short, medium, and long-term solutions.
CTR implementation	Lack of harmonisation in assessment	Approval with conditions, diverse and multiple RFIs, use of NSM (ICF), Part I/Part II interplay, non reliance on previous assessment Need to streamline the process(es) and reduce the current lack of predictability, by strengthening the role of the RMS, allowing consistent use of currently existing as well as new efficiencies / flexibilities, and applying a risk-proportionate approach for review.	Connect stakeholders to CTR Collaborate to discuss challenges and agree on short, medium, and long-term solutions.
CTR implementation	Lack of flexibility for amendments, IMPD-Q	No parallel SMs, No NSM for (all) minor changes, no flexible communication with reviewers, need CTIS workarounds for trials, IMPD-Q process A truly holistic and future-ready approach to improving the EU regulatory framework for clinical research is needed. Further flexibilities should be applied, while CTIS also requires improvement, including allocation of	Connect stakeholders to CTR Collaborate to discuss challenges and agree on short, medium, and long-term solutions. Connect issue to CTIS work
CTR implementation	Lack of harmonisation in assessment	Large number of RFIs arising following assessment of Part 1 and especially of Part 2 Perception that some NCAs may be refusing some trials in order to meet timelines or that RFIs are compilations of individual comments rather than a consolidated set of key issues focused on priorities Sponsors limit the number of MSs included in the initial application in order to reduce the number of Part 2 questions in particular Perception that MS may respond negatively or with questions of limited value in order to keep timelines Reliance on Part 1 assessment bythe Reporting Member State (RMS), for both part 1 and part 2 review by MSs remains limited Reliance on RMS Part I assessment for both Part 1 and Part 2 RFIs that relate to documents that are contained in Part 1 Focus on issues that are of significant, practical importance to participant protection Enable RFIs that can be responded to within the time limits, recognizing there may be some exceptional cases that do not fit Establish a group and mechanism for MSs and sponsor to openly share RFIs and responses where these have been to any degree challenging, albeit with some degree of anonymization if needed and develop a streamlined approach - ensuring complete good quality applications and a good, focuses and prioritized set of RFIs (where needed) for Part 1 and Part 2 Develop some points to consider to drive the lessons learned on a rolling basis	Connect stakeholders to CTR Collaborate to discuss challenges and agree on short, medium, and long-term solutions.
CTR implementation	National requirements	Local demands are still made for part 2 documents and there is no scope for a sponsor to refuse or escalate to drive alignment as per regulation.	Connect stakeholders to CTR Collaborate to discuss challenges and agree on short, medium, and long-term solutions.
CTR implementation	Lack of harmonisation in assessment	No triage of RFI is leading to inconsistent challenges for the Sponsor. Inconsistent timelines for approval processes i.e. early approval of Part II in anticipation of Part I is not advantages Empowerment of RMS to group and triage RFI should be considered to prevent contradictory RFI, support education of EC and limit expansion of scope of EC in the review process	Connect stakeholders to CTR Collaborate to discuss challenges and agree on short, medium, and long-term solutions.
CTR implementation	Lack of harmonisation in assessment	Lack of transparency in the EC's involvement in the review of PART I with some countries conducting joint reviews leading to duplicate questions or difficulty to address conflicting questions/ Linked to solution above – empower RMS to group and triage RFI Launch a EC education campaign and training	Connect stakeholders to CTR Collaborate to discuss challenges and agree on short, medium, and long-term solutions.
CTR implementation	Lack of flexibility for amendments, IMPD-Q	The inability to submit parallel amendments, and the need for protocol amendment submissions during RFI Part 1, and the impact of additional reviews required before starting studies. EU CTR timelines still present challenges in vaccines in influenza seasonality, for example, delaying Ph3 start prior Flu season.	Connect stakeholders to CTR Collaborate to discuss challenges and agree on short, medium, and long-term solutions.

Meeting Goals

- Initiate the prioritisation process using the provided Excel sheet
- Discuss the most frequent summarised issues
  - CTR implementation
  - Investigator initiated trials/Academia
  - Methodological Innovation
- Follow-up with Slido for post-meeting prioritisation





Prioritization Criteria

Importance Criteria
Critical Issue: Blocking issues impacting the initiation and conduct of the trial and severely affecting the clinical trials research environment in the EU.
Major Issue: Non blocking issues, causing delays that can be addressed with additional resources and/or workarounds
Minor Issue: Issues that indicate the need for improvement of practices and processes.

Urgency Criteria
High: Resolution within 1 year
Medium: Resolution within 2 years
Low: Resolution within 3 years or more

1- CTR implementation

- CTR implementation faces issues with inconsistent RFI handling, uncoordinated processes causing delays, and varied national requirements. This leads to fewer applications by sponsors and highlights the need for unified standards to streamline the process;
- Modify rules for submission of amendments should be implemented in CTIS, particularly important for CCT. Establish communications channels between sponsors and member states;
- A flexible risk-based approach to support low intervention, public health, pragmatic trials is needed.

2- Investigator initiated trials/academia

- Investigator-Initiated Trials (IITs) would benefit from expanding the PA2.1 mapping initiative to include broader stakeholder support, to better assist academic developers;
- IITs face high operational barriers which should be overcome, with improved training, including CTIS, on revised ICH E6 (R3), and the adoption of risk-based approaches to ease these challenges;
- IITs face limited regulatory interaction with academic sponsors, restricting early scientific advice and guidance during trial development;
- IITs face challenges from poor multinational infrastructure, lack of harmonisation (e.g. inconsistent participant reimbursement) and funding. A shift to implementation trials, cost reduction, and simplified processes are needed.

3- Methodological innovations

- The issue with RWE/D in CT is the need for flexible methodologies to better integrate these data sources. Current challenges include their underutilization, highlighting the need for adaptable frameworks to enhance their use in innovative approaches;
- Issues arise at the interface of drug and technology regulations due to unclear validation frameworks and regulatory expertise at review stages;
- Platform trials for rare diseases, like ALS, face methodological and ethical challenges, including operational, organizational, and governance issues, as well as concerns about intellectual property and data protection;
- CT including paediatric trials struggle with master protocols and innovative designs due to regulatory concerns and funding issues. Europe should be more open to new approaches to stimulate participation in innovative research.

Other topics presented for prioritisation

Regulatory and scientific advice

- Cell and gene therapies need specialized trial design advice. Pre-CTA pilot need to include EC and CTCG. High fees, limited regulatory knowledge, and inconsistent guidance affect feasibility; improved early advice and RWD use could help.
- ATMPs face regulatory challenges with separate clinical trial and GMO applications required at the MS level, leading to inefficiencies. Harmonization and consistency in the submission process across MSs are needed.
- Harmonized submission processes and better coordination between various EU regulations including CTR, MDR, IVDR, GDPR and national laws are needed for a consistent and coherent regulatory system.

Training

Specialized ATMP trial sites need trained staff and equipment. Combining regulatory with operational training and integrating EC-funded initiatives is crucial. Ongoing surveys & consultations aim to address challenges and improve site capabilities.

Patient engagement

Standardized guidance on Patient Engagement and Experience Data is essential to align regulations and prevent delays. Paediatric patients should be actively involved in trials, with early engagement to address challenges and ensure their rights are upheld.

Cross border clinical trials

Off-patent drug safety reporting is problematic due to infrequent SPC updates, leading to excessive SUSAR reporting and administrative burden. Clearer responsibility and harmonized guidance on low-grade AEs are needed to improve efficiency.

Off-patent drugs

Off-patent drug safety reporting is problematic due to infrequent SPC updates, leading to excessive SUSAR reporting and administrative burden. Clearer responsibility and harmonized guidance on low-grade AEs are needed to improve efficiency.

Access to CT data

The lack of public information on ongoing trials available for recruitment is an issue, with patient representatives calling for automated access and better tools to improve transparency and participation.

Clarifying CT Landscape

There is confusion over how various EU initiatives, like ACT EU, EHDS, and ERA4Health, fit together regarding data availability for clinical trials. Mapping these efforts is needed to address regional disparities and unlock the potential for trials across Europe.

Diversity, Equity and inclusion

Regional disparities in EU clinical trials limit access to promising therapies, especially for patients with rare or terminal cancers, resulting in delays and insufficient data on diverse populations' responses to treatments.

Embedding CTs in healthcare

Integrating CTs into standard healthcare across Europe requires greater awareness and recognition among citizens and healthcare professionals, but this priority is not reflected in the current workplan.

Ethical challenges

The integration of ethics committees faces challenges with biotech products, such as cell and gene therapies, which can raise novel ethical issues requiring specialized oversight.