ACCESS TO CLINICAL TRIAL DATA **IN EUROPE**

Lessons from EudraCT for Eudamed and the Clinical Trials Information System

TranspariMED

HAI HEALTH ACTION INTERNATIONAL

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Lessons from EudraCT for Eudamed and the Clinical Trials Information System

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INTRODUCTION

If accurate data on the design and outcomes of all clinical trials and other studies of drugs and medical devices were made public, it would help to improve clinical decision-making and patient safety, and improve the accuracy of Health Technology Assessments (HTA). This would lead to better patient care, improved public health outcomes, and the more effective allocation of public and private health resources.

Two European databases currently being developed, the Clinical Trials Information System (CTIS) and the European Databank on Medical Devices (Eudamed), could significantly improve the quantity, quality and transparency of evidence on the efficacy and harms of drugs and medical devices for many years to come. Collectively, they would reinject momentum into Europe-wide HTA reforms, and allow the European Union (EU) to better contribute to the global effort to fight COVID-19 through initiatives such as the COVID-19 Technology Access Pool (C-TAP).

However, CTIS and Eudamed will only fulfil these promises if they are well designed, effectively run, and supported by additional compliance-boosting measures.

This policy brief sets out ten commonsensical and low-cost regulatory approaches that the European Medicines Agency (EMA) and the European Commission can take to improve the quantity, quality and transparency of data on CTIS and Eudamed. Each recommended approach draws on lessons learnt from the current European trial registry EudraCT, which has been in operation since 2004.

The EudraCT Learning Curve

In 2014, sponsors' obligation to upload trial results onto EudraCT was publicly decreed without an accompanying communications strategy or support measures. Early instances of non-compliance were not followed up. Many trial sponsors remained unaware of their obligations, whilst others came to see non-compliance as normal and acceptable.

Compliance rates for newly completed trials have significantly improved in recent years. Key milestones in improving compliance include:

- the 2018 launch of the EU Trials Tracker by the Data lab at Univesity of Oxford;
- the 2019 publication of a joint letter by EMA, European Commission and the Heads of Medicine reminding sponsors of their obligations[1];
- ongoing EMA-led improvements in EudraCT user friendliness and user support;
- the sending out of reminder emails by EMA;
- continued public advocacy aimed at trial sponsors by civil society.

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[1] Even after this letter had been made public by EMA, one of the two German National Competent Authorities continued telling trial sponsors that uploading results was not obligatory. A year later, at least two large non-commercial trial sponsors in Italy continued to believe that uploading trial results was the responsibility of their National Competent Authority. This indicates that the letter was not accompanied by an adequate communications strategy.

Specific country level-action, such as pressure from Parliament in the UK, and the announcement of legal enforcement measures by the National Competent Authority in Denmark, have also led to tangible improvements.

Despite these recent efforts, around 5,900 drug trials, including around 380 paediatric trials, were still missing results on EudraCT in mid-2020. The outcome data for some of those trials has never been made public in any form, and may be considered by now as irretrievably lost, while results for many other trials are unlikely to ever be uploaded onto EudraCT, undermining its purpose as a repository for complete information on CTIMPS conducted in the EU and EEA.

In hindsight, sponsors' weak compliance with EudraCT reporting requirements over many years, and the resulting gaps in the medical evidence base, could have been avoided through better design of EudraCT itself and early decisive action by EMA and National Competent Authorities.

On the positive side, past experiences with EudraCT can enable the EMA and the European Commission to get the design and operation of CTIS and Eudamed right from the very start.[2]

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[2] The EMA and the European Commission should also systematically review the experiences of different Primary Registries in the WHO Registry Network. For example, the London-based ISRCTN trial registry has achieved significant improvements in data quality and results reporting through automated email reminders and changes to the design of its platform. Harmonised transparency rules across different trial registries and databases would help data providers to better understand and meet disclosure requirements. EMA should consider setting up a technical advisory group that involves stakeholders from other trial registries to advise on the design and operations of the results posting function in CTIS.

RECOMMENDATIONS FOR THE DESIGN AND LAUNCH OF CTIS AND EUDAMED

The recommendations below are structured chronologically into recommendations for the initial design phase and the subsequent launch phase for both CTIS and Eudamed.

DESIGN PHASE

Recommendation 1: Integrate public performance dashboards

EudraCT experience:
Clinical trial sponsors have been obliged to make public the results of certain drug trials on EudraCT since 2014. However, sponsors' compliance performance remained de facto invisible, even to many sponsors themselves, until the 2018 launch of the EU Trials Tracker revealed large and widespread compliance gaps. The tracker enables institutions to monitor their own portfolios, and external actors, such as patient groups, to identify weak performers and publicly monitor progress. Making this performance data public has helped to significantly improve voluntary compliance.

Recommendation:
Both Eudamed and CTIS should incorporate dashboards that enable users—including the general public—to assess and compare individual data providers' compliance performance, and to assess and compare aggregate compliance performance per Member State (e.g., number and percentage of medical device companies that upload all required information onto Eudamed on time, per country). There is an overwhelming public interest in full access to all available information on compliance performance. Such data should proactively be made public in accessible and comprehensible formats.

Recommendation 2: Adopt automatic data integrity safeguards

EudraCT experience:
Even though 'sponsor name' is a required data field, EudraCT currently contains over 200 trials for which no sponsor name has been provided. Equally, there are hundreds, if not thousands, of trials that have a completion date, but nevertheless continue to be listed as 'ongoing'. Such gaps and inconsistencies reduce the validity, value and utility of EudraCT data.

Recommendation:
Design the databases to ensure that data upload can either only be completed once all required data points have been entered and are internally consistent, or else to ensure that missing data and inconsistencies are publicly flagged and actively followed up until resolved. Where National Competent Authorities are involved in data streams, they should be required to act as gatekeepers to stop incomplete or clearly contradictory information from flowing into European databases. 'Closing out' a trial, file or item should only be possible if and when all required data have been provided.

Important: Eudamed will not contribute data to the WHO's global ICTRP clinical trial registry network. Listing a clinical trial of a medical device in Eudamed should therefore not be considered a substitute for prospective registration on a WHO Primary Registry or ClinicalTrials.gov (see pp. 16–17 here). For all device trials, Eudamed should contain a mandatory field for the Trial ID number issued by an ICTRP registry. Eudamed training materials should highlight the requirement for prospective ICTRP trial registration, and automatically flag any trial that was not prospectively registered on an ICTRP registry.

Recommendation 3: Normalise all names

EudraCT experience:
Sponsor names are entered into EudraCT in free text form, leading to a wide variation in sponsor name spellings. This makes it difficult for users, including sponsors themselves, to gain oversight over any given sponsor's portfolio, and difficult for regulators to contact sponsoring institutions.[3]

Recommendation:
Names of trial sponsors and all other data providers (such as medical device companies and Notified Bodies) should be automatically normalised at the data entry stage, ideally through a single institutional account that guarantees consistent naming conventions, or through a drop-down menu from which data providers can select the appropriate name out of existing registered names.[4]

Recommendation 4: Integrate automated reminder functions

EudraCT experience:
Uploading results became obligatory in 2014, and fully implemented in 2016, but EMA only started sending out reminder emails related to overdue results in 2019. As EudraCT did not reliably capture the email addresses of designated contact points at sponsoring institutions, those emails were sent to individual researchers, even though the responsibility for reporting results lies with sponsors. For thousands of trials, EMA found that it was unable to reach the researchers or other disparate points of contact as their original email addresses were no longer valid.[5] Even so, the reminder emails reportedly led to substantial improvements in compliance rates.

Recommendation:
Capture the contact data of relevant recipients and integrate automated reminders into the design of the system. Post launch, conduct A/B testing on an ongoing basis to determine the optimal timing for reminders, and the optimal wording of reminder messages.

Recommendation 5: Enable 'closing out' of all files

EudraCT experience:
Until recently, it was virtually impossible for sponsors to 'close out' trials that had ended prematurely without recruiting any participants and make this known publicly. Public data from EudraCT showed these trials as missing results, even though there were no results to report. Similar problems still exist with trials involving study sites outside the EU; from public data, it is impossible to determine whether or not their results are due. There is also no process for 'closing out' old trials whose outcome data has been irretrievably lost (for example, by marking them as 'written off'). This makes it impossible for competent authorities to comprehensively monitor compliance, and impossible for sponsors to 'close out' all due trials and take public credit for achieving full compliance.

Recommendation:
Data providers for the new databases should be able to achieve full compliance, and for that compliance to be publicly visible. This means developing pathways that ensure that every trial, file or item is unambiguously either compliant, non-compliant (and hence subject to follow-up), written off, or exempt from requirements. In addition, the design of the system should ensure that every file will eventually be permanently 'closed out' in some form or other. Adapting clear and comprehensive trial status categories can aid in this.[6]

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[3] According to a registry expert, "the University of Leuven [alone]... has at least 51 names" on EudraCT.

[4] The American trial registry ClinicalTrials.gov and its backend PRS system provide a clear model for implementing a data model in which sponsors use a single account to manage their trial portfolio on the registry, with access to the account limited to designated users. This enables the PRS team to, e.g., send lists of all trials missing legally mandated results directly to the trial sponsors concerned.

[5] "Medicines regulator unable to reach thousands of clinical trial sponsors", Research Europe, 06 February 2020

[6] The lack of an equivalent to ClinicalTrials.gov's "withdrawn" status on EudraCT has caused much difficulty for European sponsors and registry users. More broadly, it would be helpful to align CTIS (and EudraCT) status categories with equivalents in WHO's 2018 "International standards for clinical trial registries".

Recommendation 6: Harmonise data across countries

EudraCT experience:
The current EudraCT system spreads information about a single trial across individual country level protocols that could have been submitted, approved, updated, or abandoned all together at various times in the life of that specific trial. This leads to confusion over who is responsible for enforcing the trial, and what trial information is to be trusted in the inevitable appearance of discrepancies that are only resolved if and when final results are made available. This is confusing for users and hinders independent audit.

Recommendation:
The new databases should harmonise key data elements that persist across multiple countries. From there, specific country level information (e.g., enrolment, regulatory status) could be provided and validated to ensure it is consistent with the overall description of the trial. This would allow Member States to retain oversight within their countries while at the same time providing consistent and reliable data on trials and other data packages.

Recommendation 7: Clearly assign responsibilities

EudraCT experience:
In publicly available information based on EudraCT data, it is often unclear which data provider is responsible for outdated, incorrect or missing information. This creates confusion among stakeholders as to who is responsible for rectifying data issues, weakening compliance and significantly undermining accountability. For example, when completed trials remain incorrectly marked as 'ongoing', EudraCT does not allow users to discern whether the trial sponsor or the relevant National Competent Authority failed to perform their duties. Similarly, in the case of multi-country trials, different national-level trial protocols identify different sponsors, leaving unclear which of these sponsors bears responsibility for uploading the results for the trial as a whole.

Recommendation:
The new databases, accompanying guidance materials for users, and—crucially—their public dashboards (see above) should clearly identify the party responsible for performing each task, set out clear timeframes for completing each task, and provide information on whether that party has performed that task as required.

LAUNCH PHASE

Recommendation 8: Engage with small data providers

EudraCT experience:

EudraCT's lack of user-friendliness poses significant challenges for small-volume trial sponsors, leading to significant compliance shortfalls. Larger sponsors tend to have specialised disclosure staff, and therefore stronger performance. After participating in a focus group discussion with academic trial unit staff in 2019, the EMA removed compliance hurdles, notably by simplifying some processes.

Recommendation:

As a group, small-volume data providers pose the highest compliance risk. At the same time, they lack the capacity to proactively advocate for changes to the system. Conduct beta testing and focus groups with small-volume data providers and, where appropriate, adjust the system design to remove compliance barriers identified.

Recommendation 9: Instil a compliance culture from the outset

EudraCT experience:

Not challenging trial sponsors over missing results on EudraCT for many years has led to a large backlog of unreported trials. As this backlog grows, the risk increases considerably that the data will be irretrievably lost by the sponsoring institution.[7] In addition, retrospectively securing, processing and uploading missing results can be very challenging for trial sponsors, and creates a significant compliance burden. Ensuring widespread compliance from the outset would have saved the EMA, National Competent Authorities and sponsors themselves considerable time and effort and allowed the registry to live up to its primary purpose of becoming a reliable repository for clinical trial information.

Recommendation:

Instilling a compliance culture from the outset will benefit all stakeholders, including patients. The launch of new databases and the introduction of new requirements should always be accompanied by strong communication and rapid follow-up of cases of non-compliance (including offers of support), sending a clear message that non-compliance will be detected and will not be accepted. While EMA can and should conduct central monitoring and follow-up itself, it should work closely with Member States to ensure that best practices for national follow-up and enforcement are also being properly resourced and implemented at the National Competent Authority level. While local variations in such activities are inevitable, EMA should take a lead role in facilitating the sharing and rollout of best practices across Member States.[8]

Recommendation 10: Actively support compliance from the outset

EudraCT experience:

For many years, the absence of adequate guidance materials and of a functional helpdesk posed major barriers to sponsors seeking to make their trial results public. The EMA has now addressed those gaps, significantly facilitating compliance. However, helpdesk response time frames can still be slow.

Recommendation:

Actively support compliance by providing training materials and rapid-response helpdesk support from the outset. Allocate substantial resources to the helpdesk function, especially during the first year of operations, to build data providers' capacity to achieve compliance at the earliest possible stage. Adequate budgetary allocations for this function are vital to ensuring compliance in both the short and the long term because sponsors' first attempts at engagement with the databases will have a long-term effect on their future behaviour.

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[7] Note that the WHO's 2018 Pharmaceutical System Transparency and Accountability Assessment Tool recommends that jurisdictions should impose "Sanctions if [a] clinical trial is not registered and / or results are not reported".

[8] These best practices include public medical research funding institutions in Member States signing up to, and fully implementing the WHO Joint Statement. This would significantly reinforce regulatory efforts to improve transparency in medical research. At present, the majority of public funders in Member States have yet to sign up.

ABOUT THIS POLICY PAPER

This policy paper was authored by Till Bruckner, founder of TranspariMED. Five external experts, including three individuals closely involved in the management of non-EU trial registries, reviewed and commented on an advanced draft. All errors in this document are the sole responsibility of TranspariMED and Health Action International.

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