abpi
Bringing medicines to life

Points to consider when managing disclosure

This document is not a standard operating procedure (SOP) but provides suggestions and points to consider on how to optimise disclosure work and how to avoid common operational pitfalls in disclosure and transparency activities. Suggestions made are based on the experience of a variety of sponsors and includes feedback and sharing of experience of the disclosure community (eg DIA Disclosure Community, aka Disclosure SIAC).

This document covers:

- Planning disclosure activities
  - What to disclose
  - Where to post clinical trial data information
  - Posting results of clinical trials
  - Access to patient level data
  - Operational aspects
  - Company communication about disclosure
- When implementing disclosure activities
- Maintaining disclosure activities processes
- The IT aspect of disclosure activities
- Ensuring compliance with disclosure regulations
- To keep up-to-date on disclosure activities
- Special considerations
  - Working with a commercial third party (CRO)
  - Mergers, acquisitions and licensing deals

Planning disclosure activities

What to disclose

The first critical decision that needs to be made is the scope of the disclosure of clinical trial information. Country laws, the *International Federation of Pharmaceutical Manufacturers and Associations' (IFPMA) Joint Position paper*, as well as the *ABPI Code of Practice*, provide the framework and define minimum requirements. However, a sponsor company may decide to go beyond the minimum requirements. Some companies, for instance, have decided to release information about all trials (any phase, any type of design – interventional and non-interventional – and any type of participants – healthy volunteers and patients). Other companies at least disclose information about all patient trials (interventional and non-interventional, and regardless of the phase of the trial). It is important that any such decision is endorsed by senior management who will 'own' the company disclosure policy.

Scope of posting, i.e. what, when, where and how information is disclosed, is again best described in a 'Disclosure SOP'.

Where to post clinical trial data information

The second decision the sponsor needs to make is to determine on which registries information about clinical trials and their results shall be made publicly available.

Currently EudraCT information is posted by the competent national authority on the basis of the sponsor's clinical trial application. As a result of this approach, at present, the sponsor process for posting on EudraCT can and should be combined with the management of a

clinical trial application. However, trials that are conducted outside the European Economic Area (EEA) cannot be posted on EudraCT. Therefore, the sponsor will need to decide where to post public information about non-EEA trials. All registries other than EudraCT are not linked to the regulatory process and, therefore, require a separate sponsor process. The business rules and operational complexities of a given registry are highly variable and require matching process steps on the side of the sponsor.

Note, for trials conducted in the EEA the implementation of the requirement from Commission Guideline (2012/C 302/03) on posting and publication of result-related information on clinical trials in relation to the implementation of Article 57(2) of Regulation (EC) No 726/2004 and Article 41(2) of Regulation (EC) No 1901/2006 is anticipated to come into force once the EudraCT database has been upgraded.

A common approach taken by sponsor companies is to designate www.clinicaltrials.gov as the sponsor 'reference' registry. The sponsor will then need to define in its SOP (see also below) whether trials already posted on EudraCT should also be posted on the 'reference' registry. In addition, the sponsor needs to decide how local registries that may need to be considered to be in compliance with local laws/regulations will be maintained. A common approach by sponsor companies is to designate a central (headquarters based) process for posting on the 'reference' registry and delegate maintenance of local registries to country-based staff (affiliate or CRO). This approach has the advantage to overcome possible language barriers. The decision of whether a 'reference' registry should be selected, whether all pertinent registries are managed centrally or maintenance of local (national) registries is delegated to the relevant country is to be described in a 'Disclosure SOP' (see also below).

Posting results of clinical trials

Another critical decision that needs to be made is about the location for public posting of clinical trial results.

- Beside www.clinicaltrials.gov and EudraCT – however, to date the latter is entirely controlled by the regulators – most official registries do not provide the infrastructure to post results. Therefore posting of results requires the selection of a suitable platform. This can be a third party portal or a company website. Many companies use www.clinicaltrials.gov for the posting of the results of their trials. However, the level of detail required by www.clinicaltrials.gov is such that especially for smaller studies sponsored by investigators or local company organisations (affiliates) the required information may not readily be available. For this reason a number of sponsor companies have decided to maintain their own company-specific web portal, where summaries of results are posted. Typically, these summaries are written according to the formatting rules laid down in the ICH E3 guidelines.

It is recommended that the sponsor also considers challenges around the timings of posting of results; such as:

- The 'usual' definition for end of a trial is the Last Patient Last Visit, (LPLV). This LPLV may occur long after results of the first phase of the protocol – and sometimes from a medical-scientific viewpoint this may be the main phase of the trial – have been widely reported to the scientific-medical community, and even a marketing application has been filed. This typically happens in trials where survival is an important secondary endpoint and thus the 'true' LPLV is defined in the protocol as a date in a rather distant future because long-term follow-up of patients is planned, but a per-protocol analysis is performed long before LPLV in order to file a marketing application for the indication (claim) studied in the clinical trial. In such cases from a registry standpoint the trial is still ongoing but from a disclosure standpoint it would be

in line with the spirit of the disclosure policy to release details about the results in a predefined and meaningful manner at the time when the results of the first part of the trial are published in a peer review journal or used for a marketing authorisation application.

The process around the posting and publication of clinical trial results should be described in a 'Disclosure SOP'. Ensuring consistency in decision-making is critical to confirm the company's commitment to transparency.

Access to patient level data

A policy decision also needs to be made with regard to the sharing of patient level data with third party requesters. Typically, academic groups and non-profit organisations such as the Cochrane Collaboration regularly want to obtain access to patient level data to perform their own analysis and meta-analysis of clinical trials. In the context of this guidance document patient level data is defined as clinical trial data that was collected in the frame of a clinical trial for a specific patient; this includes demographic, clinical data (safety and efficacy), as well as other relevant data such as diary data. In order to share patient level data with third parties otherwise not involved in that trial (and thus not identified as recipients of that data in the informed consent form) the company must implement a robust process to remove any information that could contribute to the re-personalisation of clinical trial data. For instance, if initials and date of birth were used to identify the patient, the exact date of birth and the initials need to be replaced by a date in a categorical data format and the 'true' initials by dummy initials.

It is essential the sponsor makes a company policy decision on whether upon request or as a routine, patient level data will be shared and how it will be shared. If the company decides to share patient level data then the following aspects of data sharing should be clarified and defined in a 'Disclosure SOP':

- A definition of patient level data. Typically, this refers to per patients' listing and the full data set either as an electronic or paper output.
- Will the request of any entity – commercial or non-commercial – be considered?
- What are the criteria in terms of evidence of capability and available 'good analysis practice' which the requester needs to produce to 'qualify' for receiving patient level data?
- What does the requester need to submit in terms of an analysis, quality control and publication plan? Did the sponsor company define objective criteria to assess the robustness and scientific merit of a request for access, and conversely did the company properly define criteria to reject a request? It might be useful to have an independent body (steering committee) composed of independent experts that reviews and decides on any request for access to patient level data.
- Controls to assure adequate anonymisation of patient level data. This is of particular importance when data from older studies is shared as these data sets often contain more granular patient identifying data such as initials (rather than dummy initials), full date of birth, etc.
- Controls to assure that other sensitive data is removed. There should be a process to verify that any commercially sensitive information and other personal data is removed (e.g. names of employees).
- Timelines for responding to and satisfying a request.

The process around providing access to patient level data from clinical trials should be described in a 'Disclosure SOP'. Ensuring consistency in decision-making is critical to confirm the company's commitment to transparency.

Operational aspects

Different operational models have been implemented:

1. A decentralised model where each clinical team takes care of the disclosure tasks.
2. A centralised model where a dedicated group manages disclosure.
3. A hybrid model where clinical teams gather disclosure data and enter it into disclosure databases and the central core disclosure group manages the review, the input into the registry(ies) generated by the clinical team members and feedback from database owners.

If a sponsor mainly conducts trials in the EEA then the decentralised model has merit, as the only critical disclosure task is the posting of results. In such cases, the regulatory function often takes care of the EudraCT interface.

However, if the sponsor company is also posting trials and results on independent registries then the centralised model is more efficient and effective. Indeed, the business rules of registries such as www.clinicaltrials.gov can be complex and subject to frequent changes which represents a challenge for users that only infrequently interact with such a registry. Also aspects of quality control and quality assurance are easier to solve with a centralised model. Smaller companies conducting fewer trials may wish to consider outsourcing disclosure activities to a service provider to benefit from economies of scale and subject matter expertise of the third party.

It is recommended to capture in a disclosure data management manual the data entry and data quality rules to avoid repeat work or rejection of the posting by the concerned registry, and to document the rules applied.

Company communication about disclosure

The company should publicise through its website home page where its disclosure policy can be found. The disclosure policy should describe in lay language what is in scope of the disclosure practices of the company with regard to clinical trials, their results, access to patient level data, and also the timelines, formats and the registries which have been selected. In addition, it is useful to provide a central contact address (ideally, a contact mailing address plus a contact email address, e.g. infoclinicaltrials@company.com, is given). The company should periodically review its approach and position, and reflect this revision process in a 'Disclosure SOP'.

When implementing disclosure activities

When updating registry data (except for EudraCT), it is advisable to automate this process by linking the Clinical Trial Management System (CTMS, ie the system used for trial project management and progress tracking) with the disclosure process and software, (referred to in a later paragraph). Such linkage helps to reduce the administrative burden of the clinical team and also ensures better data quality. A review of approaches used in industry shows that a lean process that very closely matches the clinical trial application process and leverages routine tools and systems used to manage the trial results in higher efficiency and better quality. Conversely, if the disclosure process is a 'bolt on' process that requires a separate data capture flow, frequently clinical teams treat this as a low priority task and, therefore, compliance with registry business rules is often inadequate.

The company should treat this as a high priority that has senior management attention. A disclosure policy cannot be lip service but needs support, periodic review and most important an adequate budget provided by senior management.

Special attention needs to be attached to the reporting of results when a development project is discontinued, as team members designated to take responsibility generally are re-deployed to other projects. This challenge is best addressed by identifying the posting of results as a priority project close down activity and by assigning this task to a named individual. When a centralised group is responsible for posting then there is less risk that posting of results of clinical trials from terminated projects is overlooked.

Maintaining disclosure activities processes

It has already been mentioned that all registries – except EudraCT where to date the relevant health authorities assume this responsibility – require active and regular updating by the sponsor. Information such as the status of a trial, e.g. enrollment and recruitment status, clinical trial centre information, planned and effective completion date of the trial, needs to be updated at regular intervals. In general, information should be updated every month. This task is made easier if the disclosure process is interfaced with the company's CTMS.

Another task that needs attention is the assessment of a protocol amendment on the information posted on a registry. If the amendment changes information posted in the registry(ies) then the disclosure information needs to be updated once the amendment has received regulatory/ethics approval. As different registries have different posting rules the impact of an amendment on information disclosed can change from registry to registry.

Business rules of registries can change over time which requires continuous monitoring of the requirements. Some registries such as www.clinicaltrials.gov have implemented a QC process that helps those responsible for disclosure to become aware and keep track of changes that affect content of a posting. If the company has written a disclosure data management manual then this needs to be reviewed in sync with feedback received from the registry.

Companies may choose to subscribe to one of a number of commercially available clinical trial disclosure knowledge databases that offer an online resource for transparency requirements.

The IT aspect of disclosure activities

There are several commercial software offerings available that support the posting of clinical trials on registries. For obvious reasons the main focus of these software solutions is posting on www.clinicaltrials.gov. Some of these service providers also provide support in managing the operational tasks of the disclosure process.

Maintaining an in-house developed software to support the posting process is not recommended as the frequent changes of the business rules of the registry(ies) may require periodic and frequent changes to the in-house software. Any change to the software requires re-validation of the computerised system.

Sponsors submitting clinical trial information to www.clinicaltrials.gov use a web-based data entry system called the Protocol Registration System (PRS) to register a clinical study or submit results information for a registered study. The sponsor company must have a PRS

account to register study information on ClinicalTrials.gov. The sponsor can entrust a third party (service provider) to obtain such an account. Also if the CTMS of the sponsor company is interfaced with the PRS posting on www.clinicaltrials.gov is made easier.

Ensuring compliance with disclosure regulations

As a minimum a sponsor should have an SOP on disclosure and transparency that describes the scope of disclosure (i.e. which trials are disclosed, when disclosure is to take place and who is responsible for disclosure activities). This SOP should cover both the posting of trial information, as well as the posting of results and also address how compliance with the SOP as well as legal/regulatory requirements is verified, what controls are in place and what quality assurance measures are to be planned. The SOP should also describe the process to follow when a protocol amendment is implemented to assess whether the changes have any impact on publicly disclosed information. The SOP needs to uniquely assign roles and responsibilities for each disclosure task.

In addition, the sponsor should establish a process to collect performance metrics data on essential disclosure activities. The metrics should include leading performance indicators to allow the sponsor company to identify early on trials that could result in non-compliance with regulatory and legal disclosure commitments. For instance, the following parameters could be tracked, when www.clinicaltrials.gov is used as the primary registry:

- date protocol first filed with health authorities or independent ethics committee
- date protocol is registered on the applicable registry
- date first patient recruited
- projected date last patient recruited (no longer enrolling)
- date last patient recruited
- date registry is updated to reflect closed recruitment status
- date projected Last Patient Last Visit (LPLV)
- date LPLV
- date registry is updated to reflect the trial is completed
- date results are posted on the applicable disclosure site

If possible, these dates are tracked in the CTMS of the sponsor to avoid duplication of effort and inaccuracy in the tracking data. If the system does not allow for the tracking of this data then one should consider setting up a dedicated tracking tool. Metrics are reviewed periodically and corrective and preventive actions are initiated, when appropriate. As a common finding in audits of disclosure activities is the late or non-reporting of the results, it is reasonable to define an alert metrics, e.g. six months after LPLV the clinical team is asked to submit the publication plan, and then alerts are sent out in keeping with the timelines of the publication plan. If this is impractical, one elicits routine alarms at agreed time points.

To ensure that slippage of the 12 months posting deadline in www.clinicaltrials.gov is avoided or kept under control, an escalation process should be part of the metrics and also described in a ‘Disclosure SOP’.

To keep up-to-date on disclosure activities

The ABPI disclosure toolkit materials will be updated in accordance with the new EMA policy in 2014, as well as any changes introduced in the EU Clinical Trial Regulation and the ABPI Code of Practice. Those responsible for implementing the company’s disclosure SOP are encouraged to attend international conferences on the topic of disclosure and transparency. These events provide a good overview of new trends but also allow staff members newly

tasked with disclosure activities to get up to speed on the regulatory and legal requirements of disclosure.

In addition, groups such as the Cochrane Collaboration, medical journals and professional bodies host meetings and publish articles on disclosure and transparency.

Special considerations

Working with a commercial third party (CRO)

Whenever disclosure activities are not solely managed by the sponsor the contract between the parties involved should clearly identify the roles and responsibilities of each stakeholder involved, specify deliverables together with associated timelines for their delivery and quality requirements. In addition, the contract and company's SOP should be explicit about the responsibilities for tracking, verifying and documenting compliance with applicable laws, regulations, industry standards (e.g. IFPMA, EFPIA, ABPI) and company policy.

Mergers, acquisitions and licensing deals

These commercial operations are likely to affect disclosure activities and, therefore, the contract (licensing deals) or in case of mergers and acquisitions the integration plan needs to address roles and responsibilities of the parties involved with regard to disclosure.

Special attention needs to be given to the management of disclosure tasks for ongoing studies initiated prior to the completion of the deal by one of the parties. It is of particular importance that a clear common or new policy is agreed with regard to completed studies/studies terminated early and the posting and/or publication of their results. If the two companies have had incompatible or conflicting policies then a new common ground should be agreed that also addresses legacy studies.

ABPI clinical trial disclosure toolkit disclaimer

The information provided in this toolkit for companies is provided in good faith, and every reasonable effort is made to ensure that it is accurate. The toolkit is not intended and should not be construed as regulatory or legal advice. The ABPI cannot in any circumstances accept responsibility for any errors or omissions and users should satisfy themselves as to their legal obligations.