The PFMD
Book of Good Practices

All cases selected for the Book of Good Practices have been anonymised for the sake of quality control of the assessment. The Book of Good Practices showcases patient engagement projects that are exemplary in one or more PE Quality Criteria or overall show high and meaningful ways to engage and involve patients and other stakeholders in the medicines research and development continuum. The language and content reflects the views of project owners, only minimal alterations have been made to the text by PFMD to provide more clarity (when it was needed). For more information, please contact the PFMD team.

PATIENT FOCUSED
MEDICINES DEVELOPMENT

Patient organisation-led clinical trial for repurposing existing treatment

Case from a Patient Organisation (“Organisation”)

PE project description

A Patient organisation (hereafter, referred to as Organisation) led a project to start clinical trials on repurposing an existing medication to a rare disease. “It aims to study a potential new drug, called nitisinone, and assess its potential effectiveness in treating the rare disease, alkaptonuria (AKU)”.

The project started in 2003 and got European Commission’s funding in order to develop and run the clinical trials. The project is ongoing until 2019..

Which phases of research, medicines development, lifecycle or disease management does this PE project cover?

- ☐ **Research and discovery phase** 1) unmet medical needs identification, 2) disease understanding [patient experience of the disease], 3) drug discovery, non-clinical and candidate-identification phase
- ☐ **Pre-clinical phase** (including non-clinical, pre-clinical research, safety and efficacy tests)
- ☐ **Clinical study phase 1**
- ✔ **Clinical study phase 2**
- ✔ **Clinical study phase 3**
- ☐ **Health technology assessment**
- ☐ **Regulatory review and approval or registration phase** (including submitting for market authorisation request and approval)
- ☐ **Post-registration / -launch activities**
  - ☐ clinical study phase 4,
  - ☐ drug safety monitoring and pharmacovigilance,
  - ☐ Pricing and reimbursement
  - ☐ real-world evidence generation,
  - ☐ adherence,
  - ☐ patient education,
  - ☐ patient and carer support programmes,
  - ☐ disease management,
  - ☐ public health,
  - ☐ marketing insights
- ☐ **Other**

Which stakeholders does this PE project involve?

- ✔ **Patients and carers** (including caregivers, and family members)
- ✔ **Patient advocates, patient organisations and associations**
- ✔ **Healthcare professionals** (including clinical investigators, general practitioners , specialists, pharmacists and nurses)
- ☐ **Policymakers**
- ☐ **Regulators**
- ☐ **Payers**
- ☐ **Health technology assessment organisations**
- ✔ **Pharmaceutical companies or industry** (including medical devices and biotech companies)
- ✔ **Researchers** (academic researchers and investigators)
- ✔ **Research funders**
- ☐ **Other** (for example, contract research organisations (CRO) and hospitals)

1. Shared purpose

This refers to the project's aims and outcomes that all stakeholders taking part should agree on before starting the project. Consider putting in place processes to help facilitate discussions between all stakeholders to identify each other's values, expectations and objectives, and review and discuss priorities in the planning of the project. It can be valuable to enable stakeholders to exchange views openly to understand the scope and objectives of the project, acknowledging that some of their objectives may differ. All parties concerned should also have a shared written description of the common goals of the project.

Authors aimed to develop AKU re-discussion with patients (who were involved a long time) before the clinical trials (CTs) started; AKU meetings, communication towards patients. After visits, personal experience patient feedback is aggregated and presented to consortium members. Feedback is generated through a google sheets survey. (See an example of the survey and how it is presented to consortium members in Reference 1).

Workshops are a valuable tool to report back to patients about the progress of the trial and enables Organisation to address any issues if they arrive. International workshops are attended by the majority of consortium members who can address patients directly.

Communication with patients happened naturally, listening to their concerns in these discussions helped in the design and planning of the CT and making it adapt to patients' needs. A few things were changed in the design, some were compromised and some couldn't be changed based on the feedback (E.g. non treatment group).

2. Respect and accessibility

This refers to (1) respecting each other, and respectful interactions within the project to be established among partners, and (2) openness to and inclusion of individuals and communities (to the project) without discrimination. Considerations to ensure good conditions to implement the project should be made from the beginning. For example:

- simplification of wording
- budget and payment considerations
- cultural adaptations to procedures
- practicalities such as meeting timing, location and format
- accessibility of project materials
- written co-developed rules of conduct

Accessibility to participate may be facilitated by enabling multiple ways to involve stakeholders who could benefit from and/ or contribute to the project. For example, patients with cognitive impairment might need more time to go through project material, or need printed versions rather than electronic documents or PDFs for easier reading.

Patients' needs were taken into consideration in the design of the CT. This includes reducing the amount of time participants spend in each of the trial sites. Based on feedback from the project's first clinical trial, Organisation explained to other stakeholders the importance of patients having 'down time' and not staying in hospital as if they were unwell. Due to this, for the second phase of the project's clinical trial, patients stayed in a nearby hotel. Feedback from this move was overwhelmingly positive and has led to patients from across Europe seeing their visit as a holiday. They take ample opportunity to use the trip as an opportunity to explore Liverpool and its tourist sites, as well as extending their trip to holiday in the UK (See Appendix 1).

It was also noted that due to the nature of the disease, patients may have severe mobility issues. As a reflection of this, and with feedback from the patient group, it was decided that those patients will be accompanied by a chaperone who is fully reimbursed.

2. Respect and accessibility

Normally this is a family member who acts as a carer. This is vital, as patients communicated they would not come without one and allows for continuity of care.

Recruitment was efficient because patients were helping in the discussions as well (finding patients outside of Organisation's network). Understand that patients can be very motivated and a useful partner in recruiting and finding new patients. Patients understood the benefit of the trial for themselves and the patient community now and in the future. This was shown to them with reference to existing research and by a simple and accessible explanation on the trials website.

Researchers and doctors across Europe who may have patients affected by the disease were made aware of the trial by a series of email campaigns aimed either directly at them or through membership societies. Informed patients, however, would often tell their physicians about the CT. Due to the relatively low number of patients globally, these doctors are often highly specialised and have other patients with the diseases who were then informed in turn. These would become 'patient champions' who would go onto disseminate to their own national patient groups.

Ongoing surveying allows us to track how patients are feeling in regards all aspects of the trial. Monthly individual contact also adds to ongoing changes in areas that patients are concerned about based on their responses.

For example, Organisation took over paying of personal and travel expenses and booking flights for patients enrolled at the city trial site, in the middle of the trial based on feedback in regards delays in reimbursement and issues over flights. The vast majority of patients when contacted directly saw this as positive and have commended the consortium on the positive impact this has had for them.

Almost half the patient population was recruited using the steps above. Due to the nature of the recruitment, it was integral that they keep the conversation with those enrolled open at all times throughout the trial. This is reflected by the decisions taken, which are highlighted above, and by their continuing high level of retention, which is almost 95%. Very high for this type of CT.

3. Representativeness of stakeholders

This refers to the mix of people you involve, which should reflect the needs of the project, and the interests of those who may benefit from project outputs (for example, target population). Consider diversity in expertise, experience, demographics, and other relevant criteria for inclusion. When selecting PE stakeholders, patients, attention will be given to awareness of the diversity required to achieve visible representative voice.

Aiming to get everyone possible - eligible over 16 yrs old, able to travel to the site.

Some patients didn't attend due to other conditions. Approx. 60 patients from the UK couldn't join the CTs because they had taken the drug previously as unlicensed drug (National Specialised Services) >> however, they did participate in the design of the study.

Representativeness of data:

Benefit: two different data sets (60 patients from NAC) and 140 from the CT.

As per the majority of other CT's, pregnancy or imminent pregnancy was an automatic bar to enrolment due to lack of scientific understand of how the drug affects unborn children.

Project owners know of only 500 patients throughout Europe.

Project owners know of only 500 patients throughout Europe. This meant diversity was almost guaranteed. All study materials were professionally translated and the website was installed with a translation service so that it was accessible to everyone.

4. Roles and responsibilities

This refers to the need for clearly agreed, and ideally co-created roles and responsibilities, in writing, addressing that all aspects of project needs will be established upfront and revisited regularly.

- ***Organisation was accountable to the patients*** **> *workshop actions were followed up by patients***
- ***Getting EU Commission funding made Organisation accountable to proceed with the application process*** **> *having the actual EU funding held Organisation accountable***
- ***Within the project, partners held each other accountable*** ***(12 partners: 2 PGs, 1 Industry, 3 hospitals, 1 CRO, rest research teams > 5 different countries represented)***

Regular project meetings by teleconference, face to face meeting once a year, progress reports every six months.

These meetings and continued teleconferences were used to ensure that each member of the consortium knew what was expected and were accountable to everyone else.

As a patient group, Organisation is tasked with the dissemination of all the project's ongoing achievements and how it was reaching its goals. This meant that all partners had to feed back to them in regards how these goals were being met. This was then disseminated to the patient group via the project's website. If these weren't being met, Organisation held the relevant partners to account based on patient questions generated at face to face meetings.

Each partner was involved in the trial design at earlier stages and throughout. This involvement wasn't limited to the areas that they would be responsible for. This inclusivity has led to mutual ownership of the trial and where member are responsible to each other and the wider patient group.

5. Capacity and capability for engagement

This refers to (1) capacity as having relevant and dedicated resources from all stakeholders (for example, providing a dedicated point of contact by the sponsor and having allocated sufficient time by all stakeholders to allow genuine engagement); and (2) capabilities for all stakeholders to enable meaningful engagement. (For example, the level of knowledge, expertise and training stakeholders might need to deliver PE activities throughout the project).

Consider supporting stakeholders to build the required capacity and capabilities for this project in different forms of training both with sponsor organisations and with each stakeholder (for example, helping to understand the context, processes, involved terminology etc.).

Both capacity and capability building are intended to facilitate participation and lower barriers to collaborate. Stakeholders can be given access to learning resources and given dedicated support (if needed). Capability needs may vary depending on the project needs, but also e.g. personal circumstances of PE representatives.

Capacity was built almost by accident over time - Organisation's learning about the CT process alongside with patients.

Big questions from patients:

- ***Patients had their own explanations about the randomisation/ group***
- ***Placebo group problem - what's the point in it if the drug is known to already work***
- ***CT phases/ process clarified***

Suggestions from both researchers and patients were discussed openly and agreed mutually. A few workshops together, having a statistician helped in clarifying some of the questions patients had.

*The EUPATI programme is good for patient education. Educating patients on clinical research and how they are involved- 3 representatives did a EURORDIS summer school.

6. Transparency in communication and documentation

This refers to the establishment of communications plan and ongoing project documentation that can be shared with stakeholders. Communication among stakeholders must be open, honest and complete. In addition, adequate up-to-date documentation must facilitate communication with all stakeholders throughout the project. Consider proactively and openly sharing progress updates throughout the project externally. In addition, communicating outcomes of the project to all stakeholders and how their contribution was of value to the success of the project is critical.

Documentation is part of the EC grant requirements - every 18 months.

- *Making sure patients know what's going on to ensure retention (interim communications after phase 2, midway phase 3)*
- *Every month all patients emailed for questions or update with information.*
- *For the CRO, this level of communication was unusual.*
- *Partners happy to have discussions about how much can be shared.*
- *Need to understand different stakeholders' motives to keeping some of the information confidential.*

Communication:

- *Comms (related to CT) to patients has to go through the ethics committee*
- *Advice received from CRO on transparency and communication with patients (documents needed, what can be said and not, how to explain things)*
- *Ongoing discussions about patient support after the trial is over*

7. Continuity and sustainability

This refers to the smooth progression of the project, as well as efforts to maintain ongoing relationship with stakeholders. Consideration should be given for the role of stakeholders beyond a single project. When starting the project, consider including in your project plan the actions needed for maintaining expected flow of the project from beginning to end. Create a plan to nurture relationships with your partners and stakeholders involved during the project, and when needed and requested, beyond the project as well. For all stakeholders successful planning and personal and organisational resilience should be anticipated.

Continuity:

- ***EC project requires study reports, documentation for licensing***
- ***Patient survey for patients taking the drug on why they're taking this drug should help in discussion with payers***

As a patient group, Organisation has a vested interest in the continuation of the search for an effective treatment for alkaptonuria. If this trial is successful they will liaise with all concerned in regards licensing of the drug and reimbursement across the world. They will assist patients enrolled on the study to find healthcare and treatment after the study. Any further discussion on this isn't appropriate at this stage.

Positive impact for specific medicines development phases

Discovery and research: identifying unmet medical needs, prioritise research agenda.

Clinical development phases: improving study design (e.g. fewer protocol amendments), accelerating patient recruitment, improved retention of the patients during clinical studies, reduced time of the clinical development of the medicine, financial impact.

Registration: quality of registration dossier, timing to registration.

Post launch - life cycle: patient solutions increasing patient adherence to medication, extension to new patient groups, adapted formulation, enhanced quality of AE monitoring and reporting, etc.

- First treatment to AKU
- No major amendments to the study protocol.

Efficiency: Faster recruitment (under 1 year vs. 2 years) due to prepared patients

Direct or indirect positive impact for patients

Finding treatment for alkaptonuria patients.

- Recruitment rate 50% of eligible patients across Europe
- Retention rate over 95%

Direct or indirect positive impact for stakeholders involved in the project (other than patients)

Researchers: understanding patients' unmet medical needs, PE helps in focusing and prioritising research efforts, research funding process is empowered with patient insights.

Patients/ Carers: influence/ impact to research prioritisation agenda, easier access to novel therapeutic options (e.g. new medicine in clinical trials phase), influence on outcomes of clinical trials, enhanced understanding of disease conditions and treatment options, better compliance to treatment.

Wider community: more effective medication leading to reduced health services, health/ condition related education of one individual is shared beyond that individual.

Patient Advocates/Patient Organisations: increased knowledge about being involved in collaboration with other stakeholders.

Industry: more effective research prioritisation efforts, acceleration of clinical development, faster registration process, etc.

HCPs: better understanding of patients' health conditions and expectations, quality of clinical trials, adherence to medication is increased, etc.

Regulators: patients' voice is embedded is decision-making, ensuring the quality of the regulatory file etc.

- Reducing the time that patients had to spend at the site

Funding: all partners received funding from EC in this project

- Pharmaceutical company hopefully will end up with an approved product at the end of the study

Hospital site: Came up a new method to measure HGA (chemical in AKU patients) and therefore monitor progression of AKU → Papers/ research articles published

Lessons Learned

Since the beginning of the project, Organisation has shared what it has learnt across a myriad of media, from articles to talks. This is due to the rarity of projects like this. Organisation was learning every step of the way. Luckily with the help of the pharmaceutical company the clinical sites and the CRO, along with the drive of Organisation to represent patients, Organisation believes it has designed a remarkable CT.

As Organisation leads on patient identification, recruitment and support for all patients enrolled at the three clinical sites across Europe and also leads on dissemination of the project, project owners were in a unique position to give advice to others in a similar situation.

- Relationships: it's integral to build relationships with patients, to help them understand everything about the trial and feel able to ask the difficult questions. This is the key reason for including patient groups in clinical trials. Pharma companies have to keep their distance from patients, and so patient groups can fulfil that role.
- 61% of patients said feeling part of a community was an important part of deciding to take part in a trial. Rare disease patients are so spread apart, communities have to be online to get the discussion going with the most patients.
- 30% of clinical timelines is to recruit patients for research and 90% of clinical trials are delayed because of patient recruitment problems; this is made even more difficult in rare diseases. However, in this project they reached target of almost 150 patients in under 9 months. Through hard work, and collaboration, media campaigns across Europe, attendance at scientific conferences, and email campaigns to 7,000 specialist doctors.

References

1. http://patientfocusedmedicine.org/wp-content/uploads/2018/05/Attachment.xlsx

Appendix 1 - 2016 Feedback (Liverpool)

CLINICAL TRIAL 2

Overall experience? Average of 4.5

The travel organisation? Average of 4

The accommodation? Average of 4

The interpreter? Average of 4.5 (four answered this question)

The organisation of tests and Assessments? Average of 4

Communication with staff prior to visit? Average of 4

During visit? Average of 4.5

After visit? Average of 4

COMMENTS

Negative

- Patients prefer the Liner over other hotels.
- Some patients wish to go home on early and feel like they are not needed for the whole time.
- Taxis being late/not turning up in Liverpool.
- Expenses issues.
- Having to go back to departments due to mistakes.
- Mixed reviews of interpreters in Liverpool.

Positive

- The staff in Liverpool are widely praised by patients, especially Emily and Ranga.
- High score for overall experiences staff and organisation
- High praise for communication before during and after visit.

OBSERVATIONAL STUDY *

*Only three patients responded.

Overall experience? Average of 4.5

The travel organisation? Average of 4

The accommodation? Average of 4.

The interpreter? N/A

The organisation of tests and Assessments? Average of 4

Communication with staff prior to visit? Average of 4

During visit? Average of 4.5

After visit? Average of 4.5

COMMENTS

Negative

- Ear Biopsy did hurt. One patient said it hurt a lot, the other two thought it was an acceptable level of pain. Suggestion strong painkillers are provided.
- Slight delay in expenses.

Positive

- High score for overall experiences staff and organisation
- High praise for communication before during and after visit.
- Liverpool staff and Patient Organisation are highly praised

- "Everyone was great! Which eased a lot of my concerns."
- "Thanks you guys, seriously. It means a lot to be treated like a human being especially during trials."