Patient Reported Outcomes

MHRA PRO-SIG & PGCF 2nd November 2021

Medicines & Healthcare products Regulatory Agency

Patient Involvement Strategy

- Our Patient Involvement Strategy was published at the end of September 2021, and patient/public consultation informed its development at every step.

- It has five core components which are all essential to its successful delivery, and the role of partnership working is one of these strands.

- We’re at the early stages of our journey and are committed to making fast and effective progress to better meet the needs of patients.

Patient Involvement Strategy

Involving patients and public

- We're introducing clear processes to involve patients more systematically and reviewing our committees and groups to have consistent patient representation and meaningful involvement in our work

Responding to patients and public

- Customer Service Centre provides a single point of contact for patients, public and other customers to contact us. The Safety Connect will improve the user experience of Yellow Card,

Driving culture change

- Our new vision, values and behaviours including one focused on patients, e-learning programmes for all staff on what patient involvement means to them in their role and how to bring it to life, and our public Board sessions which invite patient involvement and questions on our work

Building Partnerships

- Our Patient Group Forum is being overhauled & expanded to be truly representative of the patient population. We're keen to build an insight sharing capability with partners to meet the IMMDSR recommendation to "Collect once, Use often".

Measuring outcomes

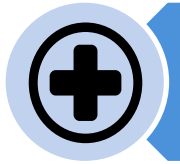
- We have measures built in to understand how well we're doing in changing our culture as well as in delivering our patient focus ambition. This considers the outcomes for the three broad patient groups, informed by in-depth analysis from across the organisation

Delivering

Enabling

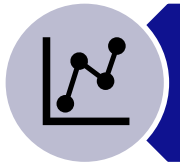
Evidencing

What are PRO(M)s?



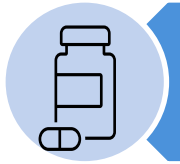
PRO is an umbrella term covering both single dimension and multi-dimension measures of symptoms, HRQL, health status, adherence to treatment and satisfaction with treatment

A PRO includes any outcome evaluated directly by the patient himself or herself and is based on patient's perception of a disease and its treatment(s)



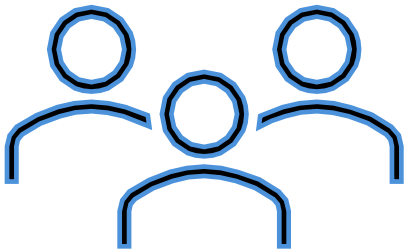
Using data generated from PROs provide a systematic way of measuring patients' views about their health and wellbeing.

Patient-reported outcome measures (PROMs) are the tools used to measure and collect data on PROs.



PROMs are focused on real benefits achievable for the patients.

PRO – Special Interest Group (PRO-SIG)



A multidisciplinary team within the agency with expertise in PROs has formed a PRO Special Interest Group (PRO-SIG)

Focus on the benefit for patients

The aims are:

- Gain an understanding of existing knowledge and expertise of PROs within the agency,
- expand on that knowledge
- raise awareness of the importance of good quality PROs in research and drug development

100 colleagues replied to an initial survey with a good spread of staff in different roles and across the agency, demonstrating the strong interest

Identify training needs, need for more guidance

IMMDSR Report

Government report on how the healthcare system in England responds to reports about harmful side effects from medicines

Strong emphasis on the importance of collecting more widely and routinely health outcomes as perceived by the patient – Patient Reported Outcome Measures e.g. health-related quality of life

These should become common currency in the assessment of benefits and risks

Agency's strong commitment to becoming a 'patient-focused' regulator

IMI SISAQOL

- SISAQOL-IMI (Setting International Standards of Patient-Reported Outcomes and Quality of Life Endpoints in Cancer Clinical Trials – IMI) is an international multidisciplinary consortium, co-led by the European Organisation for Research and Treatment of Cancer (EORTC) and Boehringer Ingelheim (BI)

- The consortium has been set up to generate recommendations to standardize the use, analysis, and interpretation of patient reported outcome (PRO) data in cancer clinical trials

- SISAQOL-IMI will establish guidance on how to use patient-reported outcomes in cancer clinical trials so that they can be used in a methodologically sound way, analysed in a statistically adequate manner, and intelligibly presented to ensure a high study quality and a better comparability of results across clinical trials

FOCR – Broadening the definition of tolerability

- Regulators define tolerability as “the degree to which overt adverse effects can be tolerated by the subject” (ICH E9)
- Does not emphasize the patient experience, lacks focus on how adverse events can be best evaluated from the patient’s perspective
- Clinician-reported outcomes and case report data are routinely collected to assess the safety and tolerability of a therapy – still important
  - But these provide limited understanding of the full scope of tolerability from a patient’s perspective
- *A* new working definition has been proposed that incorporates the patient experience by measuring treatment burden and patient-reported symptomatic toxicity and function

‘The tolerability is the degree to which symptomatic and non-symptomatic adverse events associated with the product’s administration affect the ability or desire of the patient to adhere to the dose or intensity of therapy. A complete understanding of tolerability should include direct measurement from the patient on how they are feeling and functioning while on treatment’

Real world data collection

- Lots of interest in using real world data to support regulatory decision making e.g. Adaptive pathways, IMI GetReal, EMA registries project, true life cycle approach to evidence generation

- Information about how a patient feels and functions, as captured directly from patients themselves is often missing in real world data

- PRO collection has been limited e.g. PROs were collected in only 14% (*n* = 8/57) of recent post-authorisation safety studies [Engel et al., 2016]

Without PRO data, real-world evidence will not actually reflect how real patients experience real therapies in the real world

- Lack of standardisation and the need for international collaboration to develop the required tool kit to consistently complement real-world data with PROs

Nature Reviews Drug Discovery: Harnessing the patient voice in real world evidence: the essential role of PRO

EMA Appendix 2: PRO measures (April 2016)

- **Problem statement:**

Poorly defined PRO objectives & methodology in drug submissions have traditionally hampered the usefulness of PROs in regulatory decision making

- **Key aim:**

By outlining broad principles of scientific best practice rather than prescribing a particular approach to PRO selection and application, the appendix aims to encourage developments in the methods and application of PROs in the oncology regulatory setting

- **Key message:**

The importance of the patient's point of view on their health status is fully acknowledged and such information may be used in drawing regulatory conclusions regarding treatment effects, in the benefit risk balance assessment or as specific therapeutic claims

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

1 April 2016
EMA/CHMP/292464/2014
Committee for Medicinal Products for Human Use (CHMP)

Appendix 2 to the guideline on the evaluation of anticancer medicinal products in man

The use of patient-reported outcome (PRO) measures in oncology studies

Draft agreed by Oncology Working Party	December 2013
Adopted by CHMP for release for consultation	22 May 2014
Start of public consultation	17 June 2014
End of consultation (deadline for comments)	30 November2014
Agreed by Oncology Working Party	November 2015
Adopted by CHMP	1 April 2016
Date for coming into effect	1 November 2016

Keywords	***Patient-reported outcome (PRO), health-related quality of life (HRQL)***

Innovative Licensing and Access Pathway overview

- **ILAP was launched 1st of January 2021**

- **Innovation Passport:** A new medicine designation links to the development of a roadmap to patient access

- **Target Development Profile** (TDP): Creates a unique UK roadmap, utilising tools from a toolkit and providing a platform for sustained mutli-stakeholder collaboration
  - Dedicated section on Patient and PRO
- **A toolkit**: tools are intended to drive efficiencies in the development programme, supporting data generation and evidence requirements

- **An integrated pathway**: Pulls together expertise from across the MHRA, NICE and SMC and partners in the wider healthcare system including the NHS in England and Scotland

How are data on PROs collected?

- PROs are measured with questionnaires or surveys that are either:
  - completed by the patients themselves,
  - completed by the patient in the presence of the researcher, or
  - completed by the researcher through face-to-face interview or by telephone interview.

- PROs data can be collected electronically (using ePRO technology) or paper-based

- The modality used to collect PROs data can affect the quality and completeness of the data

PROs in Clinical Trials – Data collection

- PROs have been around for many years - but usually not a main outcome of interest in trials
- Often added as a secondary objective – sometimes many different PROs
- Often offered at many time points with no clear view of which time point should be prioritised
- Usually suffer from a lot of missing data as not a clear priority

PROs in Clinical Trials – Data collection

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4

PROs in Clinical Trials - Analysis & interpretation

- When we assess the efficacy of a medicine we want to avoid false positives
- It is therefore very important to pre-specify the exact endpoint and analysis to be carried out

“If you torture the data long enough, it will confess.” — Ronald H. Coase

- Usual endpoint seen in protocols: Quality of life
- We really need something like: change from baseline to month 6 in total score for domain X using instrument Y

PROs in Clinical Trials - Missing data

- Usually more missing data for PROs than any other endpoint
- A recent COVID-19 trial had over 40% subjects with missing PRO data at day 7
- Makes PRO results useless – not representative of whole population

- By focusing on time points and domains of interest this could be improved
- Patients should not be given questionnaires unless clearly useful

- Might help if patients understand the importance of certain time points and domains? Can focus on these if too many questionnaires?
- Patients could also help understand reason for missing data

PROs in Clinical Trials – Improvements needed

More clarity from investigators on exact outcome of interest and at what time point(s)

- How this will be analysed
- What data are needed from the patient
- Nice to know Vs Need to know Data
- More effort to reduce the missing data
- Understanding reasons for missing data
- More patient engagement

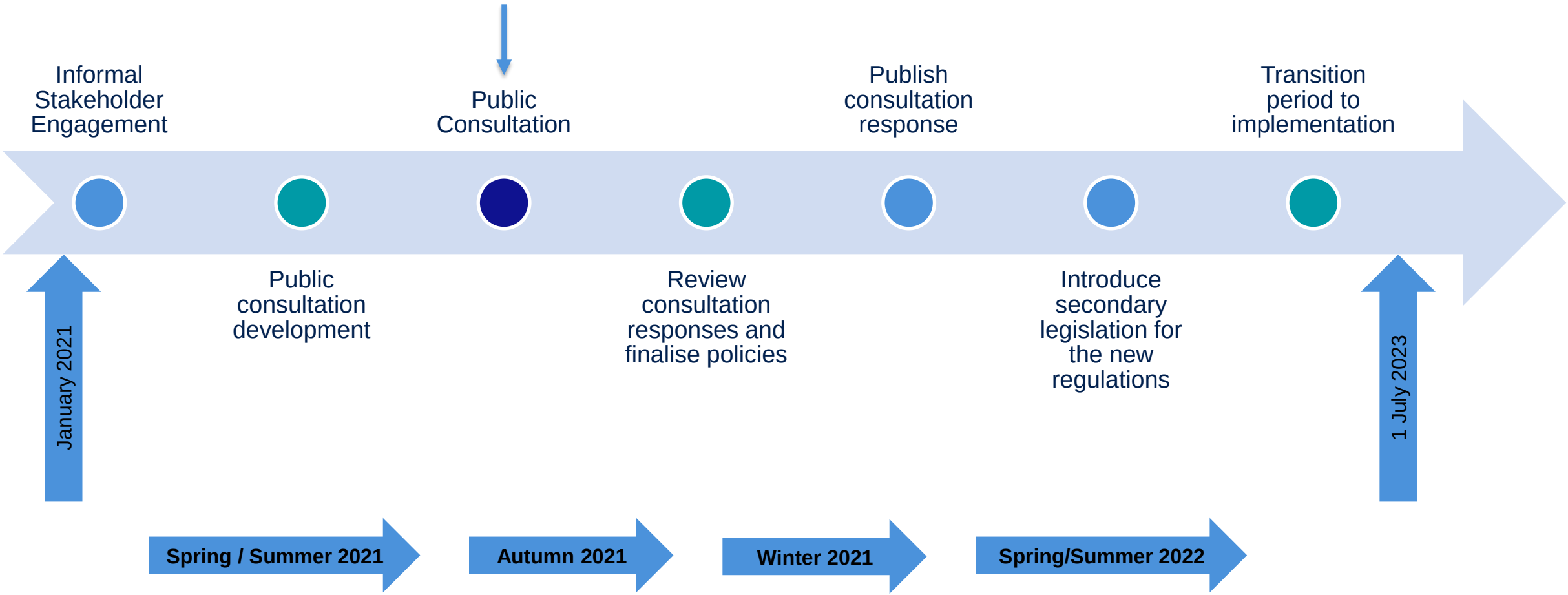
Medical Devices - Our aim

A robust, world-leading regulatory system for medical devices in UK that prioritises patient safety.

A system that….

1. Prioritises patient safety
2. Enables access to innovative medical devices
3. Has enhanced trade and international collaboration
4. Swiftly detects and responds to problems with devices effectively and proportionately
5. Is agile - adaptive to a fast changing market

Indicative timeline and key milestones



Consultation Chapters 13 – 17

Chapter 13: Environmental sustainability and public health impacts

Chapter 14: Routes to Market

Chapter 15: Transitional Arrangements

Chapter 16: Feedback

Chapter 17: Questions for members of the Public

Next steps

The consultation closes on 25 November 2021 at 11:45pm

MHRA will then collate and analyse all responses and begin to identify emerging themes

Once analysed, we will publish a response to the consultation

MHRA will use the information gathered to inform our legislation

Regulations to be in place by 1 July 2023

Do you think MHRA should have additional guidance on PRO(M)s?

What should that be?

How would you want to be involved?

What else could we be doing?

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