Hardian Health

Innovate UK

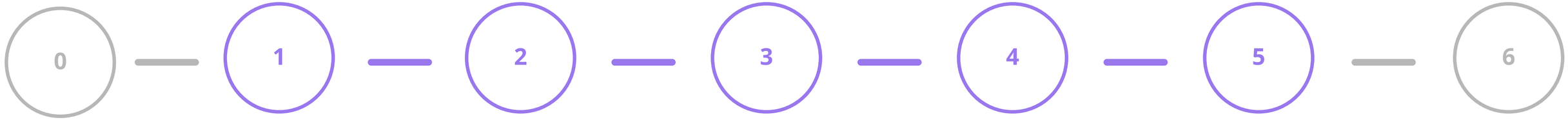
Health Innovation Network South London

Module 7: Compiling Clinical Evidence

Outline

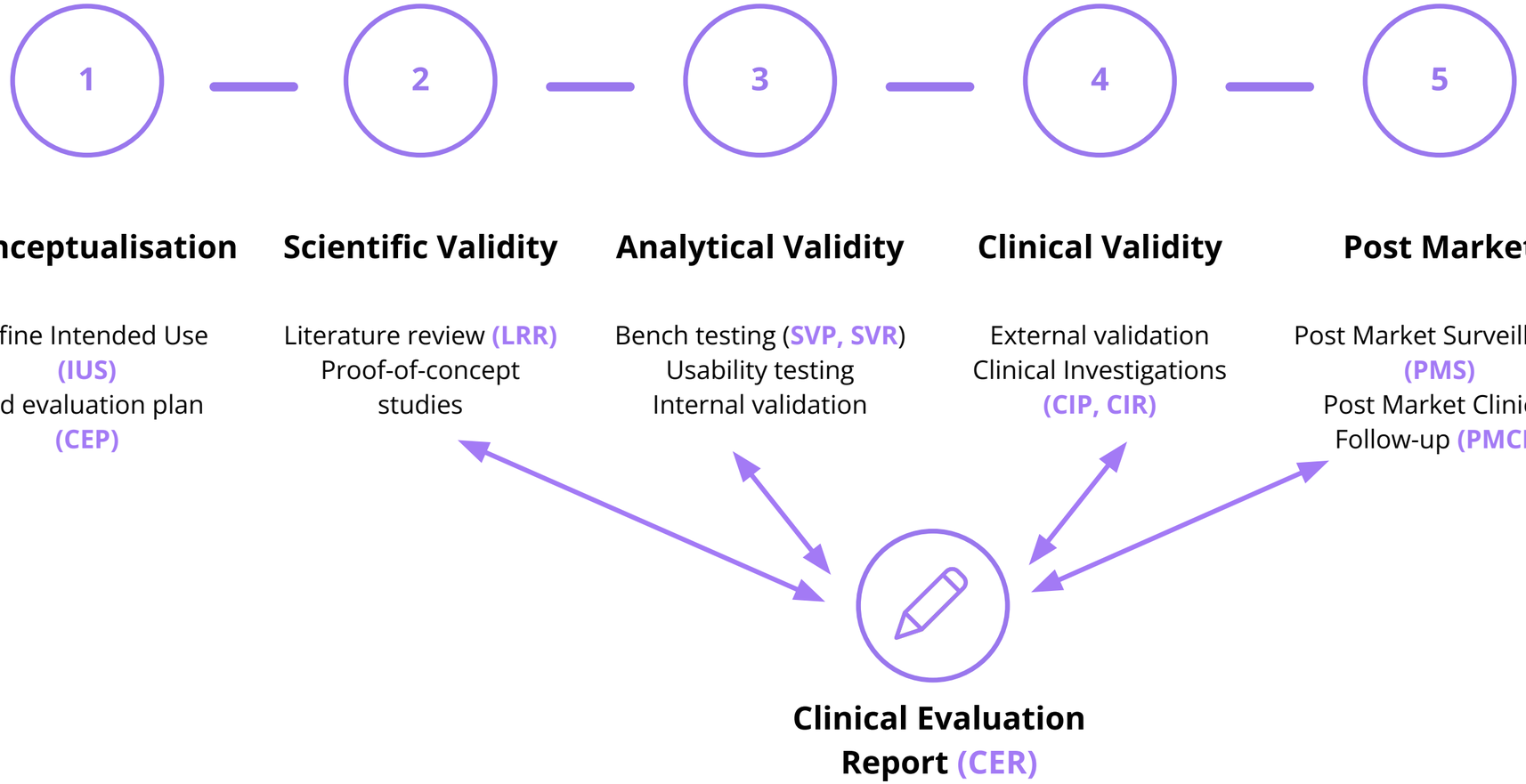
1. Recap the Clinical Evaluation Process from Module 6
2. Outline documentation requirements from conceptualization, all the way to post-market
3. Multiple Choice Questions

Clinical Evaluation Process - Overview



0	1	2	3	4	5	6
Define Value	**Conceptualise**	**Scientific Validity**	**Analytical Validity**	**Clinical Validity**	**Post Market**	**Deliver Value**
Define Unmet Need Value Proposition	Define Intended Use (target market, condition, users)	Literature review Proof-of-concept studies	Bench testing Usability testing Internal validation	External validation Clinical Investigations	Post Market Surveillance Post Market Clinical Follow-up	Demonstrate Economic Value

Clinical Evaluation Process - Overview



Write your Intended Use

Document the following

Intended medical indication

Intended patient population

Intended user groups (primary and secondary)

Intended part of the body

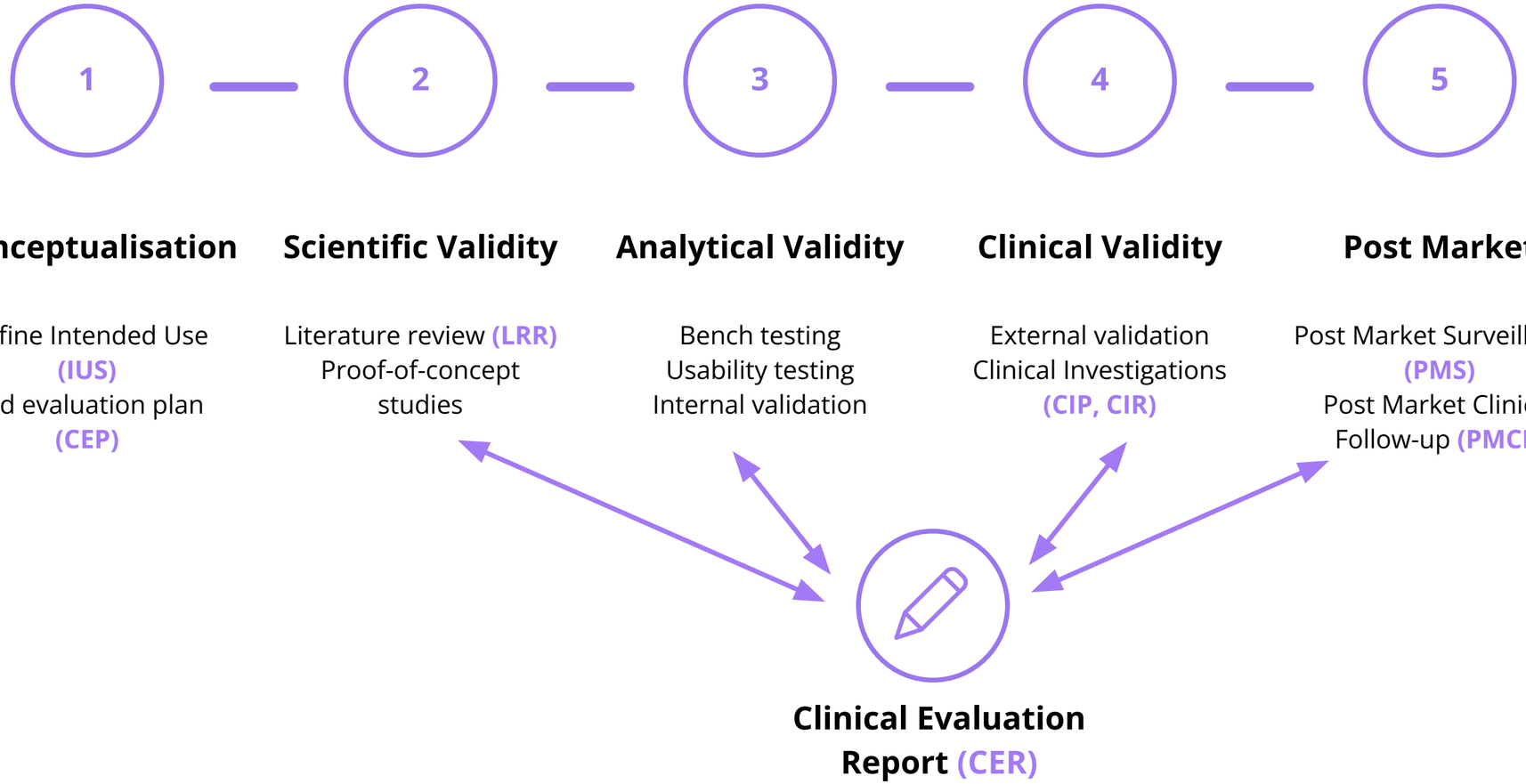
Intended use environment (physical and digital)

Operating principle (clinical and technical)

Foreseeable misuse

Risk classification

Clinical Evaluation Process - Overview



Write your Clinical Evaluation Plan

A high level overview of your entire clinical development plan

State your clinical benefit

Describe how you intend to demonstrate

Scientific validity

Analytical validity

Clinical validity

Post-market clinical follow-up

Set milestones and acceptance criteria for moving onto the next stage of clinical evaluation

Demonstrating Scientific Validity: Literature Review

General points to cover

Is your technology based on sound scientific principles?

How well does your approach work?

Who are your commercial competitors?

What is the current clinical gold standard?

What are the gaps in the literature? i.e. what studies do you need to do?

Look out for best practices in investigation design

Sample sizing

Control/comparator arms if needed

Validated outcome measures and endpoints (both clinical and statistical)

Gold standard/current standard of care clinical practice

PRISMA Guidelines

PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	

Literature Review Report (LRR)

Findings

Tabulate all results with reasons for inclusion / exclusion

Tabulate performance benchmarks for clinical practice, SotA and any competitors

Include any risks identified

Conclusion

Answer the question - is there a valid scientific association between our claim and the literature?

What is that association, and how strong is the evidence?

What performance metrics are we aiming to prove?

What are the common methodologies for investigations in this use case?

What are the evidence gaps we need to demonstrate?

Literature Review - Tips

Record your search terms and methodology

Ensure consistency across reviews

Enable others/new hires to conduct the review if required

Review search terms regularly to include State of the Art

Maintain a competitor analysis matrix

Must be documented to feedback into adverse event reporting, risk register and evidence requirements

You must repeat your literature review annually

Minimum requirement criteria under the MDR

Must include any and all publications relating to your device, whether positive or negative

Good practice is to repeat the searches 3/6 monthly, and hold an internal clinical review to include/exclude any new studies

Analytical Validity

- Product requirements and risk registers (PRR)
- Software verification plans and reports (SVP, SVR)
- Risk management plans and reports (RMP, RMR)
- Cybersecurity/data protection plans and reports

Clinical Investigation Plan (CIP)

Evaluate and document the risks and benefits of proceeding to investigate an experimental technology

Justify the design of the clinical investigation

Document the Investigator's Brochure, Case Report Forms and Informed Consent procedures, and a monitoring plan for adverse events

Follow protocol headings in ISO 14155

Clinical Investigation Plan (CIP) - logistics

Select your partner sites and clinical trials units (CTU)

Agreements with partner sites - outlining clinical, data and risk management responsibilities

Consider the need for:

Establishing a data monitoring committee for higher risk investigations

Ethical approval: IRAS / HRA

Regulatory exemptions: MHRA

Clinical Investigations: ISO guidance (BS EN ISO 14155)

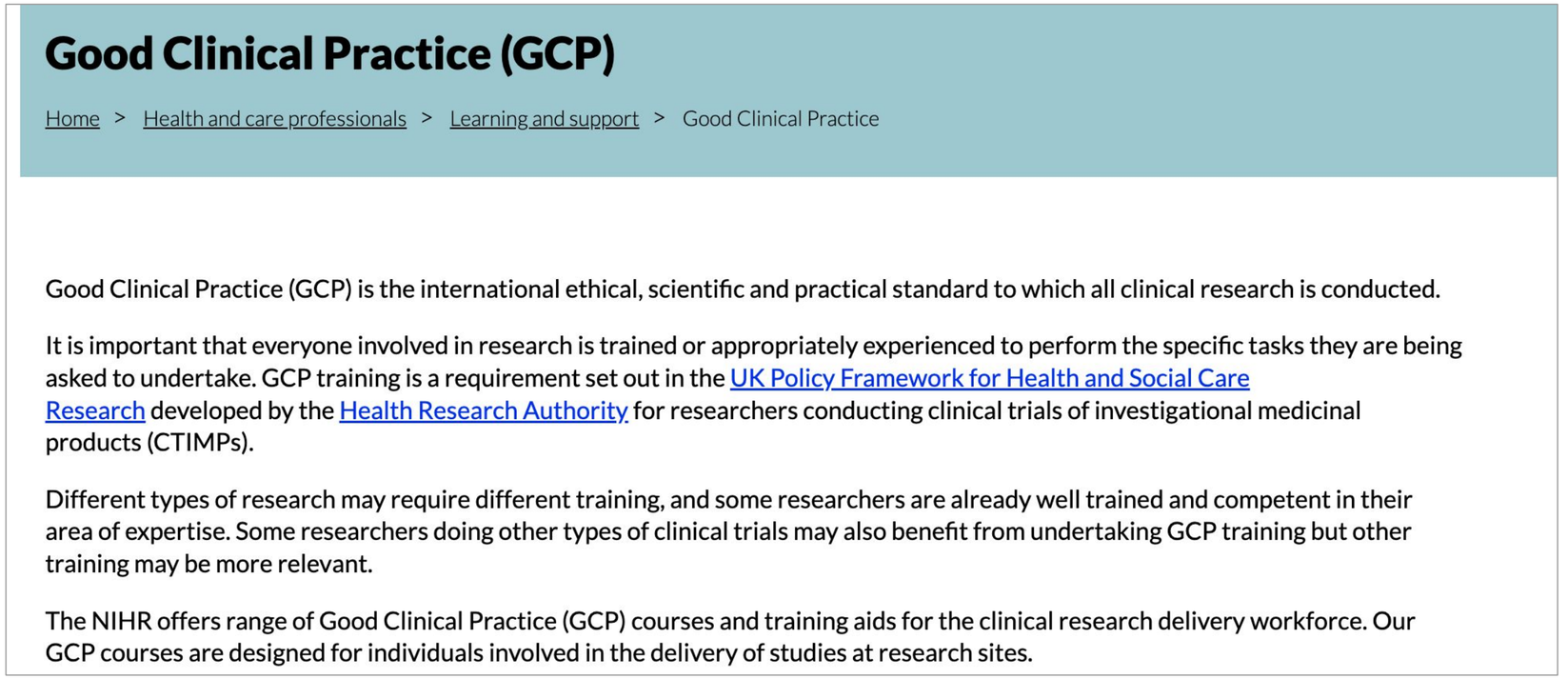
Purchase the standard (auditors will check!)

Read the standard - you cannot comply with it unless you know what it says

NIHR Good Clinical Practice - GCP

Complete the course

Or hire someone who is experienced in designing studies in line with it = “GCP trained”



Good Clinical Practice (GCP)

Home > Health and care professionals > Learning and support > Good Clinical Practice

Good Clinical Practice (GCP) is the international ethical, scientific and practical standard to which all clinical research is conducted.

It is important that everyone involved in research is trained or appropriately experienced to perform the specific tasks they are being asked to undertake. GCP training is a requirement set out in the UK Policy Framework for Health and Social Care Research developed by the Health Research Authority for researchers conducting clinical trials of investigational medicinal products (CTIMPs).

Different types of research may require different training, and some researchers are already well trained and competent in their area of expertise. Some researchers doing other types of clinical trials may also benefit from undertaking GCP training but other training may be more relevant.

The NIHR offers range of Good Clinical Practice (GCP) courses and training aids for the clinical research delivery workforce. Our GCP courses are designed for individuals involved in the delivery of studies at research sites.

Regulatory Investigational Device Exemption (IDE)

- **Submit investigation protocol via IRAS**
- Submit design control documentation
- Pay the fee
- Conduct investigation
- Submit quarterly summary reports

Guidance

Notify the MHRA about a clinical investigation for a medical device

UK

How to notify the MHRA of your intention to carry out a clinical investigation for medical devices.

Investigational Device Exemption (IDE)

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Send Medical Device eSTAR and eCopy Premarket Submissions Online

October 3, 2022 - The FDA is announcing that you may now send electronic copy (eCopy) or electronic Submission Template And Resource (eSTAR) premarket submissions online through the CDRH Customer Collaboration Portal ("CDRH Portal").

Building on the progress tracker for 510(k) submissions launched in 2021 and the trial process of electronic uploads launched in July 2022, the CDRH Portal now allows anyone to register for a CDRH Portal account to send CDRH eCopy or eSTAR premarket submissions online.

Starting October 1, **2023**, all 510(k) submissions, unless exempted*, must be submitted as electronic submissions using eSTAR.

USA

An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. Clinical studies are most often conducted to support a PMA. Only a small percentage of 510(k)s require clinical data to support the application. Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE **before** the study is initiated.

Clinical Investigation Report

Detailed, traceable and accountable documentation is vital

Often not reported to auditable detail in standard academic publications (not using investigational product)

Documentation of adverse events and risks

Regulators care about **safety** and **risk** as much as performance

Must give indication of what needs to be followed up post market

Follow report headings in ISO 14155

Post Market Plans

Post Market Surveillance (PMS) Plan

Who is going to conduct the activities?

How frequently are you going to check?

Who will be responsible for addressing any shortcomings?

Post Market Clinical Follow-up (PMCF) Plan

What type of PMCF will you need? (continuous vs discrete study)

How many participants will you recruit?

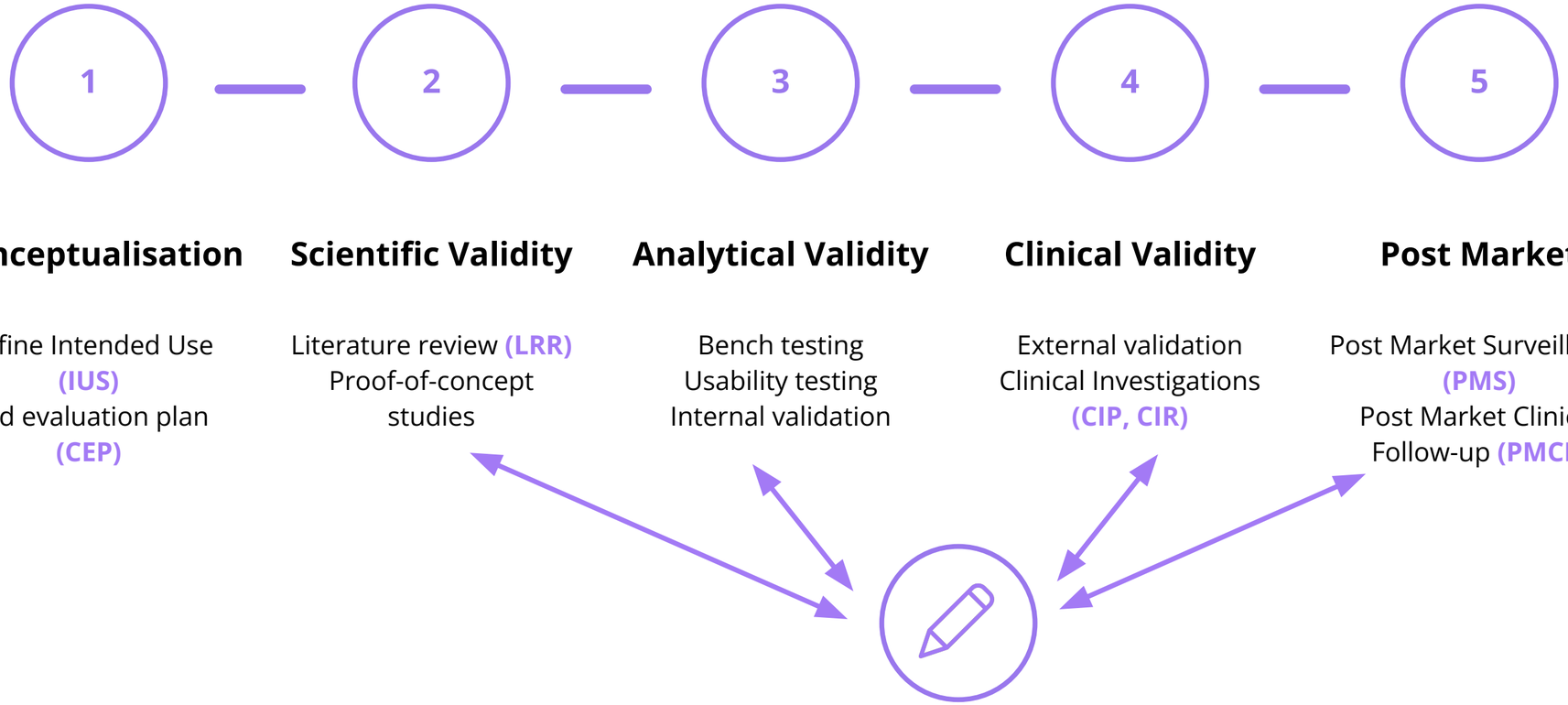
From which sites?

What are the endpoints going to be?

PMS and PMCF can be combined into a single document - but all aspects must be covered!

Clinical Evaluation Report (CER)

A documentation of your **entire** clinical evaluation process



Clinical Evaluation Report

A summary of the Intended Use, Benefits and Risks

Describe the product, its limitations and contraindications, and any risks associated with it

A compilation of all evidence

Summary of the literature review and current state of the art in solving your clinical problem

Collation of all the evidence you have collected pre-market (and eventually post-market)

Summary of all the hardware and software verification and validation activities, and results from usability studies

Demonstration of how you meet the general safety and performance requirements

And a plan for how frequently you will update the literature review

Clinical Documentation Summary

1. **Intended Use Statement (IUS):** *what is the product?*
2. **Clinical Evaluation Plan (CEP):** *how do you plan to prove its clinical benefits throughout the product life cycle?*
3. **Literature Review Report (LRR):** *demonstrate scientific validity (± proof of concept studies).*
4. **Clinical Investigation Plan (CIP):** *how do you plan to prove clinical validity (study protocol)?*
5. **Clinical Investigation Report (CIR):** *demonstrate clinical validity.*
6. **Post Market Surveillance Plan (PMS Plan):** *how do you plan to monitor safety post-market?*
7. **Post-Market Clinical Follow-Up Plan (PMCF Plan):** *how do you plan to monitor clinical effectiveness post-market?*
8. **Clinical Evaluation Report (CER):** *a summary compilation of all the above.*

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