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psephos BIOMEDICA

Strategic Approaches to Clinical Data Gathering: *from concept through commercialisation and beyond…*

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Agenda

1. Setting the clinical strategy
2. Designing the right study for the right development stage

- Using data from all sources to support
  - Regulatory submissions
  - Marketing claims
  - Patient benefit

Q&A

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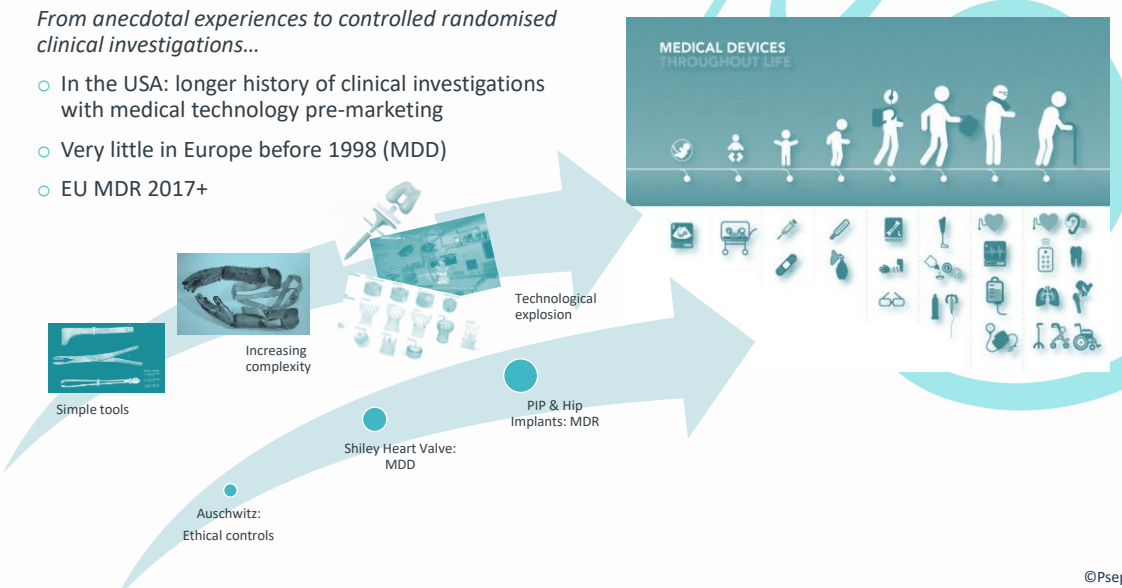
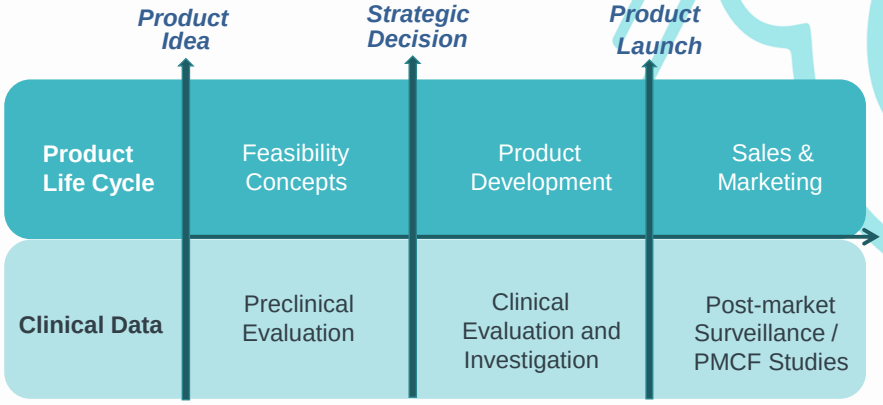
1.1 Why clinical evidence?

From anecdotal experiences to controlled randomised clinical investigations…

- In the USA: longer history of clinical investigations with medical technology pre-marketing
- Very little in Europe before 1998 (MDD)
- EU MDR 2017+



1.2 What clinical evidence? Product life cycle phases



1.3 What drives clinical strategy development?

Regulatory

- CE Mark, FDA or other jurisdiction
- Manufacturer defined vs prescriptive direction
- Clinical "phases"
  - Pre-clinical literature review, animal model studies, SOTA
  - Proof-of-concept / First-in-human
  - Pilot study
  - Pivotal study
  - PMCF Study (registry, etc.)

Reimbursement

- Economic data gathering
- Market access (countries)
  - UK: NICE / DE: DRG-NUB / USA: CMS

Marketing & Sales

- Early adoption:
  - KOLs
  - Proctors
- Study publications
- Evidence for marketing claims
- Conference presentations
- Case study and/or live case

Design & development

- Usability / human factors assessment

Funding

- Restrictions / commitments made to grant providers
- De-risking for capital investment
- Strategic corporates

1.4 Real world clinical strategy issues

- Do we really need a clinical investigation?
- What is the least number of patients we can enrol?
- What is the shortest possible end-point we can reach?
- How can we gain economic data for the device?
- Can we publish data at a conference?
- Would it be possible to broadcast a live case at a congress?

What's legal, ethical & acceptable for patients?

- Regulatory & clinical: the company conscience
- Balancing regulation with economic reality
- *The magistrate test*
- *The loved one test*

1.5 Clinical strategy/development plan

Answering the relevant clinical questions by:

- planning,
- developing and
- implementing

a clinical evidence gathering plan that

- generates sufficient detailed data, and
- that is achieved within both economic realities and ethical considerations.

MDR: a clinical evaluation plan must include:
"a clinical development plan indicating progression from exploratory investigations, such as first-in-man studies, feasibility and pilot studies, to confirmatory investigations, such as pivotal clinical investigations, and a PMCF …with an indication of milestones and a description of potential acceptance criteria"

- Clinical proof of concept (FIH)
- Pilot [CE Mark study: MDD]
- Pivotal (FDA & CE Mark study: MDR)
- PMCF (e.g. registry, etc.)

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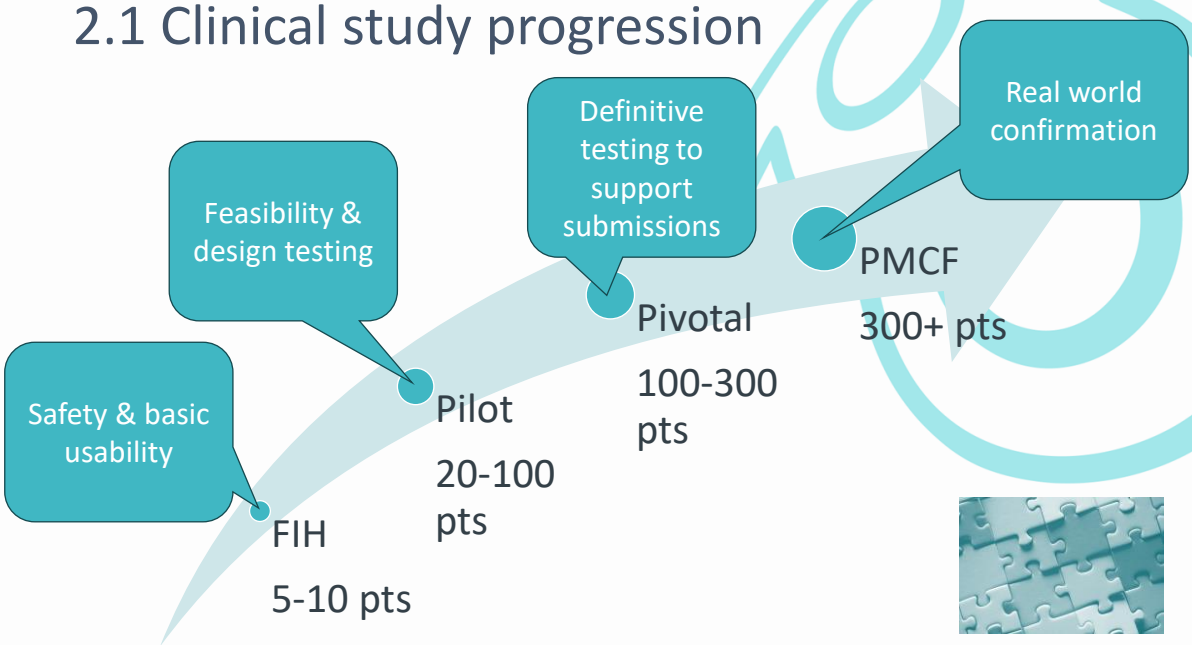
2.1 Clinical study progression



2.2 Purpose of each type of study

FIH	Pilot	Pivotal	PMCF
Initial Safety and Feasibility: Aim to test a new medical device in **humans** for the **first time** to evaluate its initial **safety, feasibility**, and performance.	**Feasibility:** Conducted to assess the **feasibility** of the device, its **safety**, and to gather preliminary data on its **efficacy**.	**Definitive Testing:** Designed to provide **robust evidence** on the **safety and efficacy** of the device to support **regulatory approval**.	**Real-World Users:** Involves patients/users using the device in **routine clinical practice**, which should be a **broader and more varied population** than in pre-market trials.
Basic Functionality: Assess whether the device works as intended in a human clinical setting.	**Design Testing:** Assist to **refine** the device's **design** and the trial **protocols** before larger-scale studies.	**Regulatory Submission:** Data from these trials are used to submit to regulatory authorities (e.g., FDA in the US) for market approval.	**Confirming Risk-Benefit:** Gathers further data to support the **risk-benefit conclusions** over a **longer period of time**.

2.3 Outputs from each type of study

FIH	Pilot	Pivotal	PMCF
Initial Safety Data: Focused on establishing the **basic safety profile** and identifying any **immediate adverse events**.	**Expanded Safety Profile:** More comprehensive understanding of the device's **safety in a larger population**.	**Regulatory Submission: Results** are used to seek **approval from regulatory bodies** (e.g., FDA, EMA) for market introduction.	**Post-Market Surveillance:** Contribute to ongoing **PMS**, ensuring **continued safety and effectiveness** of the device.
Basic Feasibility and Functionality: Ensuring the device **works as intended** and can be **used effectively in a clinical setting**.	**Preliminary Efficacy and Operational Feasibility:** Gathering **initial data** on the device's **efficacy and validating the feasibility of future study**.	**Clinical Acceptance:** Provide the evidence needed for the **medical community to adopt** the device in clinical practice.	**Regulatory Compliance:** Support regulatory requirements for **continued monitoring and reporting of device performance**.

2.4 Clinical investigations: design concepts

Must be designed to:

- verify that under normal conditions of use the performance characteristics of the device are those intended by the manufacturer; and
- determine any undesirable side effects under normal conditions of use and assess whether these constitute risks when weighed against the intended performance of the device.

So, pre-commercial studies:

- Phase "IIa"
- Prospective?
- Rarely blinded
- Safety & performance endpoints
- Follow-up

Randomised Clinical Trials?

- The gold standard…
- Maybe with creative approach (e.g. 2:1 randomisation)
- Dependent on the ethics of patient treatment: may be cross-over
- Randomisation sometimes not possible: mitigate bias

2.5 Design of each type of study

FIH	Pilot	Pivotal	PMCF
Exploratory Nature: These trials are **highly exploratory** and often involve a **single-arm** study without a control group.	**More Structured:** These trials **may still be single-arm** but can also include **control groups**, depending on the **study objectives**.	**Controlled Trials:** Typically involve **RCTs**, with **control or comparison** groups (e.g., current standard of care).	**Observational Studies:** Often designed as **observational** studies, including **prospective** or retrospective cohort studies, **registries**, or **case series**.
Endpoints: Focus primarily on **safety endpoints** (e.g., incidence of adverse events) and **basic performance** metrics.	**Endpoints:** **Primary endpoints** focus on **safety**, while **secondary endpoints** gather **preliminary efficacy** data.	**Endpoints:** Clearly defined **primary and secondary endpoints**, focusing on **clinically meaningful outcomes** related to **safety and efficacy**.	**Endpoints:** Focus on **long-term safety**, **device performance**, **user satisfaction**, and any **newly identified risks or benefits**.

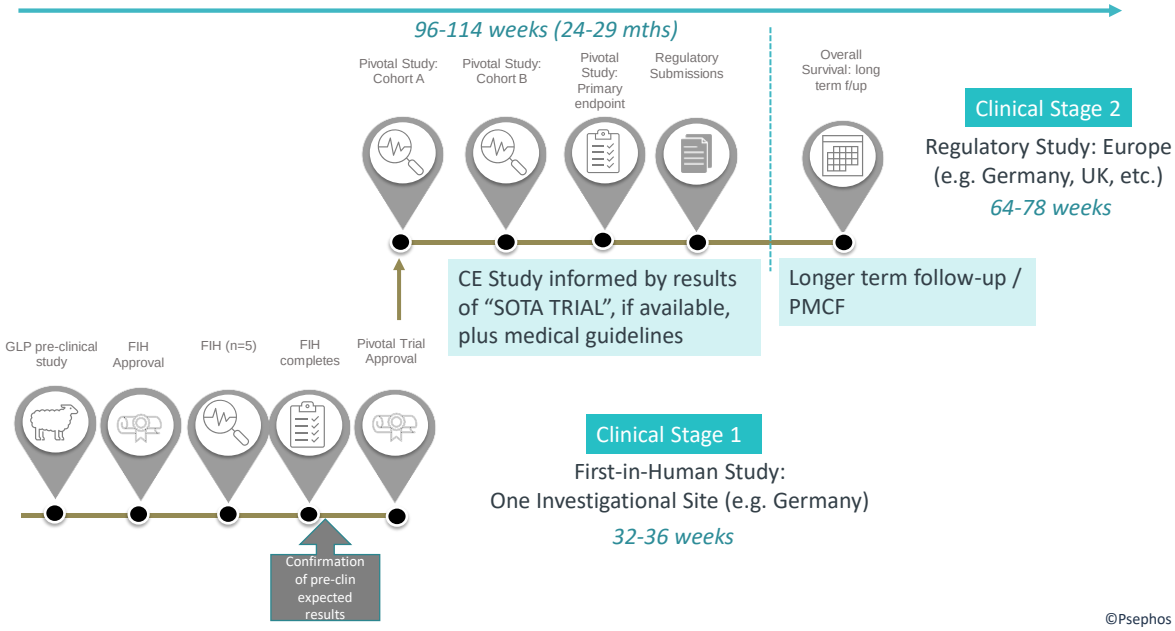
2.6 Overall clinical strategy: example

- Single centre prospective FIH feasibility / safety study (n=5)
  - <<Treatment>> and surgical study (based on most recent similar study)
  - Safety established
  - Confirm animal results extrapolate to human clinical use
- Multi-centre prospective Pilot-to-Pivotal performance and safety study (n=180 with stopping rules from n=100)
  - Technical success immediately post-treatment
  - Technique success at 3 months f/up
  - Stage 1 (Pilot) – up to 30 pts with 30d safety gate => Stage 2

2.7 Pilot-to-Pivotal: potential endpoint design

	Stage 1 (Pilot - Cohort A)	Stage 2 (Pivotal - Cohort B)
Primary Endpoint		
- Technical success immediately post-ablation	Y	Y
- Technique efficacy at 3 months	Y	Y
- SAEs at 30d post-treatment	Y	-
Secondary Endpoint (A)		
- SAEs at 30d post-ablation	-	Y
Secondary Endpoint (B)		
- Follow-up / Imaging at 6, 12, 24 & 36 months	Y	Y
- Overall survival and/or disease survival	Y	Y

2.8 Proposed Clinical Pathway



2.8a Clinical strategy: FIH

- Single centre prospective FIH feasibility and safety study
  - Patients with malignant peripheral lung lesions that are suitable for <<treatment>> and are deemed suitable for surgical resection
  - 5-10 patients
  - Procedural, safety and histological endpoints
- Learning from <<SOTA Trial>>:
  - Stage I - II primary lung cancer - solitary pulmonary nodules ≤3cm.
  - CT to evaluate radiological changes 2 - 4 weeks after <<treatment>> (30d).
  - Surgery to remove the lung nodule and histopathology of tissue.

2.8b Clinical strategy: Pilot

- Multi-centre prospective performance and safety study
  - Patients with biopsy proven malignant, or radiologically suspicious lung nodules who either are not surgical candidates due to comorbidities/high surgical risk or have declined surgery.
  - Able to tolerate single lumen endotracheal tube intubation for the procedure, under general anaesthesia.
  - Lesions should have a maximal diameter ≤3cm, at least 5mm away from major blood vessels (>3 mm in diameter).
  - Endpoints:
    - Procedural success
    - Change in <<treatment>> zone volume at 12m
    - Safety at 12m
  - Additional potential benefits to explore as endpoints:
    - shorter overall inpatient hospital stay;
    - reduced postoperative pain;
    - reduction in pleural-based complications.
  - Sample size: 30 patients?

2.8c Clinical strategy: Pivotal

- Multi-centre prospective randomised performance and safety study
  - Patients with biopsy proven malignant, or radiologically suspicious lung nodules who either are not surgical candidates due to comorbidities/high surgical risk or have declined surgery.
    - Control group: Medical management standard of care
    - Treatment group: <<Study device>>

    1:2 randomisation and/or cross-over design
  - Lesions should have a maximal diameter ≤3cm, at least 5mm away from major blood vessels (>3 mm in diameter).
  - Endpoints:
    - Procedural success
    - Change in <<treatment>> zone volume at 12m
    - Safety at 12m
  - Additional potential benefits to explore as endpoints:
    - shorter overall inpatient hospital stay;
    - reduced postoperative pain;
    - reduction in pleural-based complications.
  - Sample size: dependent on potential delta in treatment outcomes driven by results of Pilot study and historical data on medical management standard of care [Bayesian design with stopping rules?]
  - *Survival rates at 5 years post-procedure PMCF*

2.9 Where should we run our studies? (1/2)

- FIH
  - Experienced user / good research team
  - Accessible for company
  - Right patients are available
  - Ethical speed to initiation / completion
- Pilot
  - Experienced user / good research team
  - Accessible for company
  - Right patients are available
  - Patient compliance to follow-up regime
  - “Standard” medical practice

- FIH
  - UK
  - EU
  - Australia
  - Eurasia
  - USA (EFS)
- Pilot
  - UK / EU
  - Australia
  - USA (EFS)
  - Canada

2.10 Where should we run our studies? (2/2)

- Pivotal
  - Mix of experienced users / research team & upcoming sites
  - Accessible for CRO
  - Right patients are available in right quantity
  - Patient follow-up compliance
  - Standard of care
- PMCF
  - Users of all levels of experience
  - Real world patients
  - Longer term (less intensive) follow-up

- Pivotal
  - UK / EU
  - USA (EFS)
  - Canada
  - Australia
- PMCF
  - Key markets

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