Engaging companies in academic trials of ultra-rare (UR) tumours

Hopes and hurdles

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Approvals in UR sarcomas

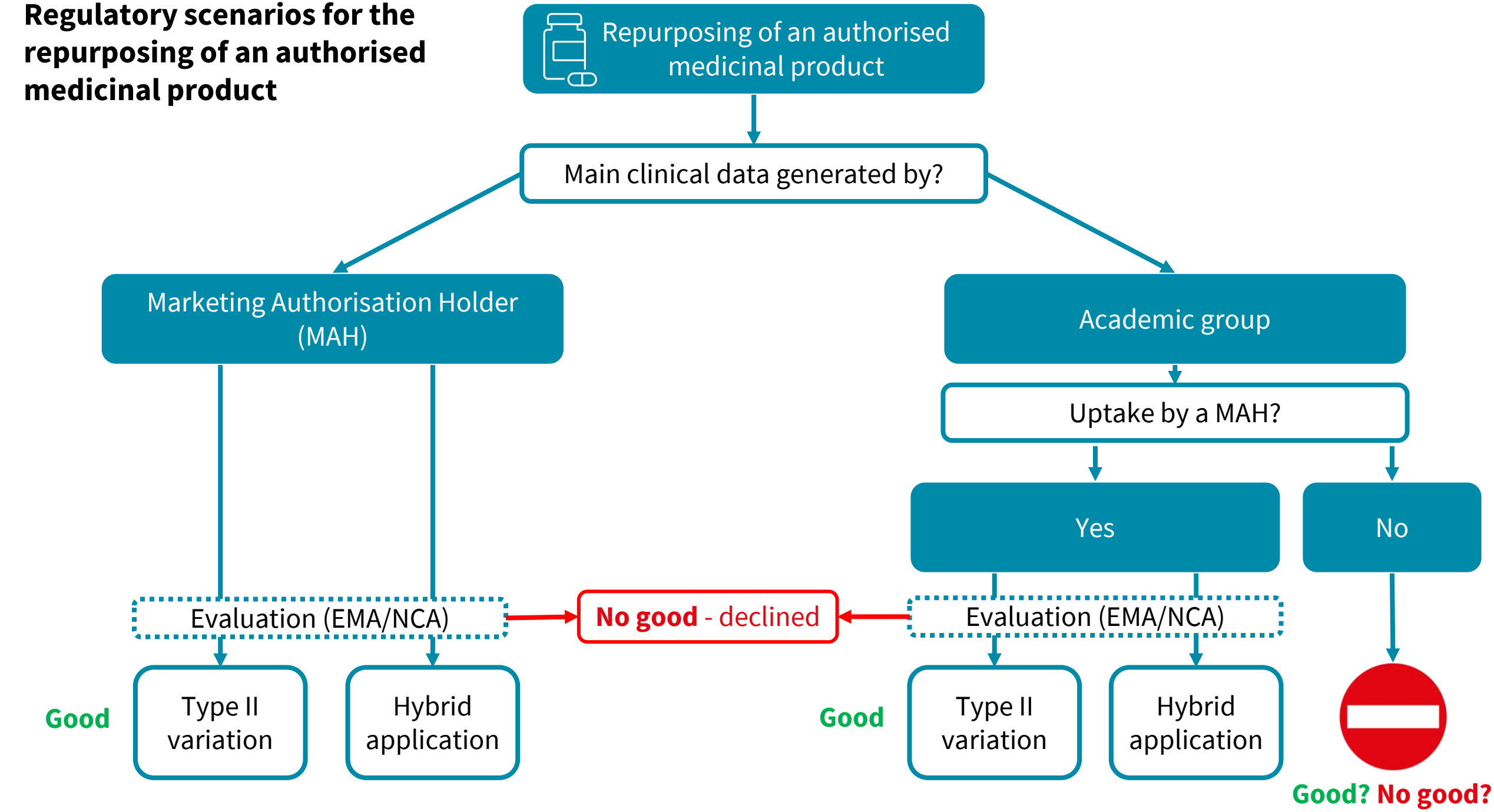
Drug	Indication	First MA or '*Repurposing*'	EMA	FDA	Trial name	Sponsor
Crizotinib	IMT	Repurposing	Yes	Yes	ADVL0912	COG
Atezolizumab	ASPS	Repurposing	No	Yes	NCI-2016-01040	NCI
Pexidartinib	TGCT	First MA	No	Yes	ENLIVEN	Daiichi Sankyo
Avapritinib	GIST (PGDFRA D842V)	First MA	Yes	Yes	NAVIGATOR	Blueprint Medicines
Tazemetostat	Epithelioid sarcoma	First MA	No	Yes	EZH-202	Epizyme
Nab-sirolimus	PEComa	First MA	No	Yes	AMPECT	Aadi Bioscience

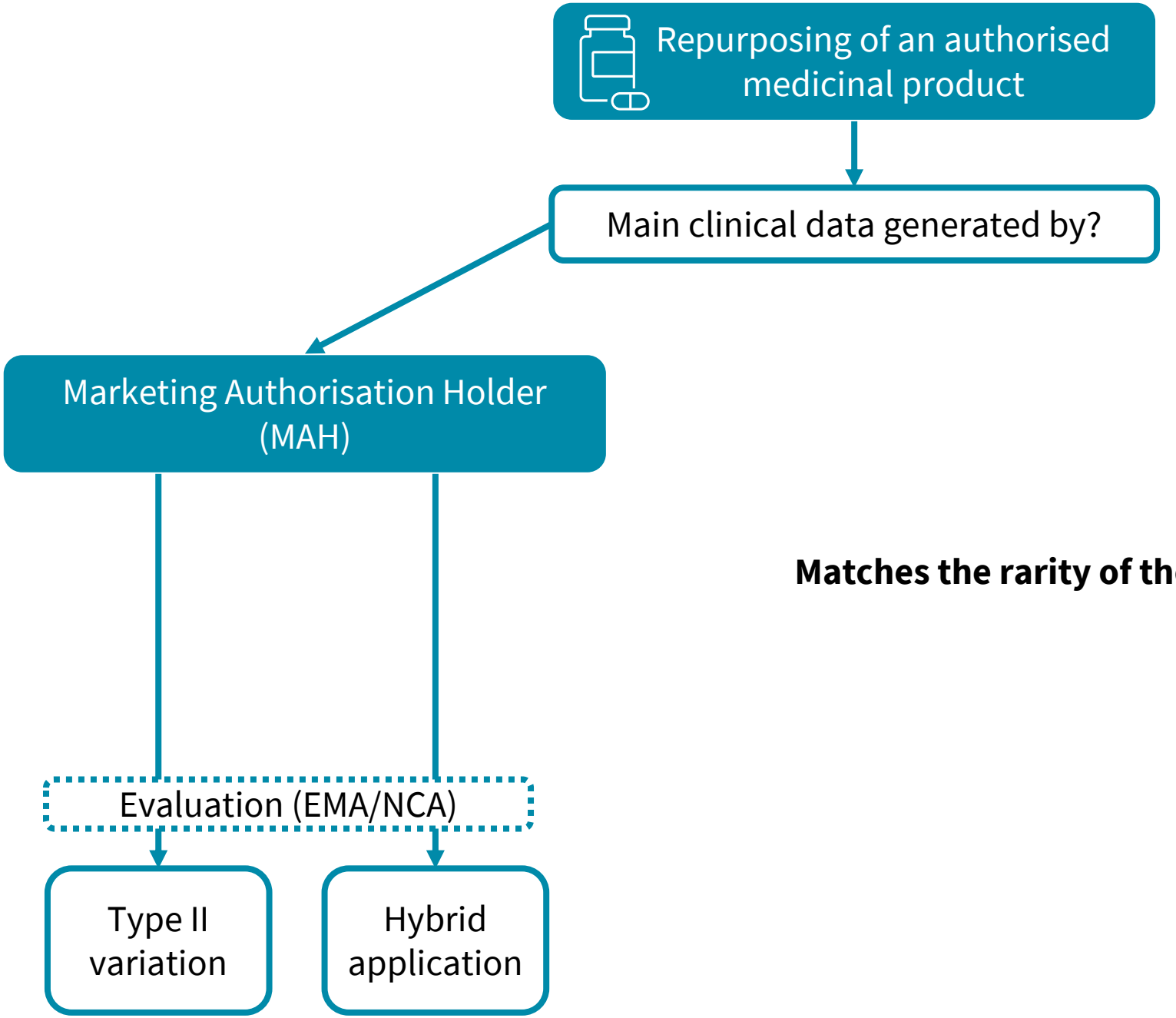
Why are UR approved drugs rare?

Main issues	Barriers related to issue
Rarity of the disease	Limited number of patients
	Limited patient involvement
	International trials required
Drug manufacturers' position	Little or no apparent interest to pursue any ultra-rare indication
	Little or no interest to provide investigational medicinal product for an investigator-initiated trial in ultra-rare cancer
	Uncoordinated strategy from both companies and academic trialists when multiple drugs targeting the same pathway exist
Academic trials in regulatory submissions	Limited regulatory experience by drug companies using academic trials in submissions
	Request for extension of indication must be submitted by market authorisation holder.

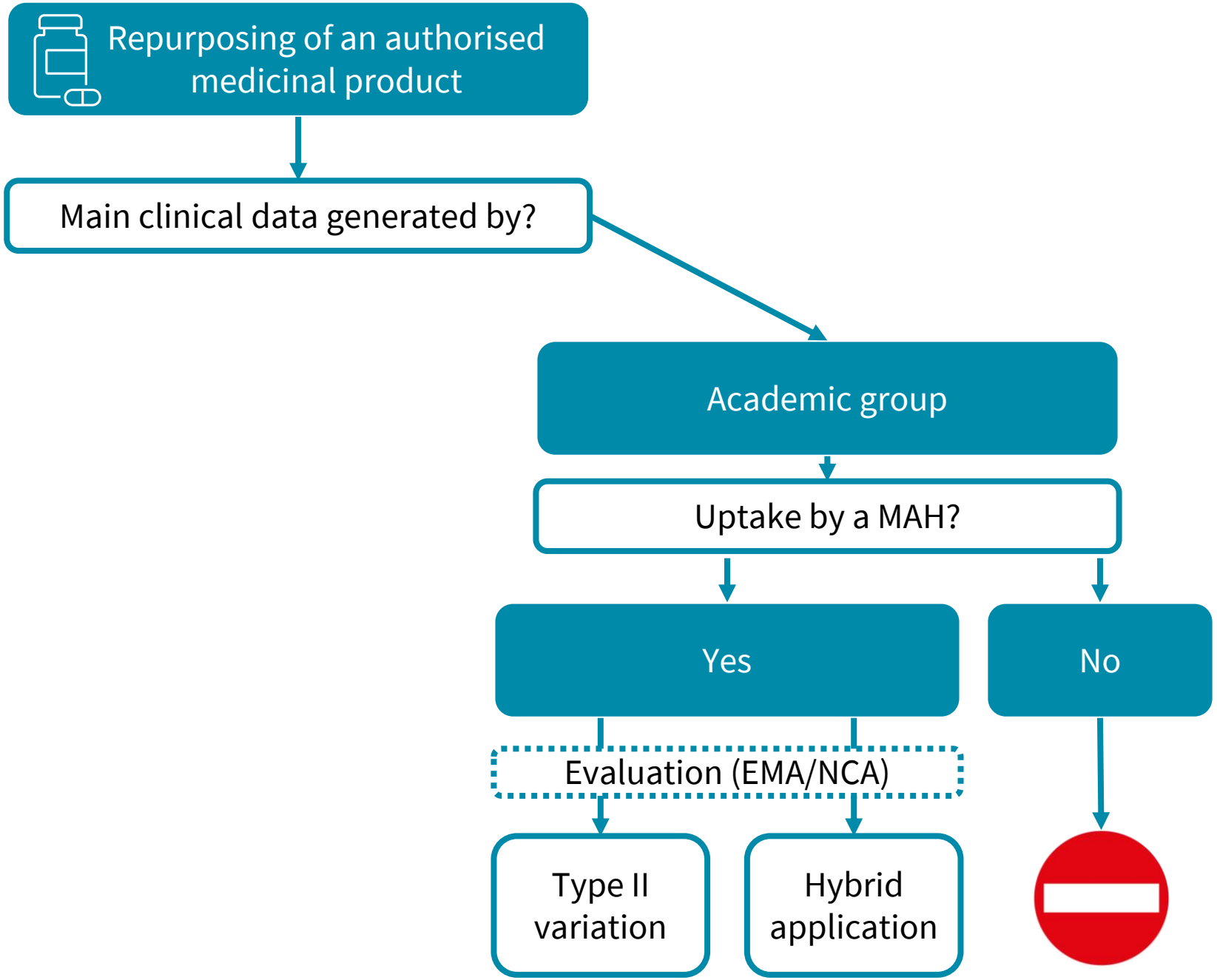
Adapted from Stacchiotti & Bouche 2024 Eur J Cancer

Regulatory scenarios for the repurposing of an authorised medicinal product

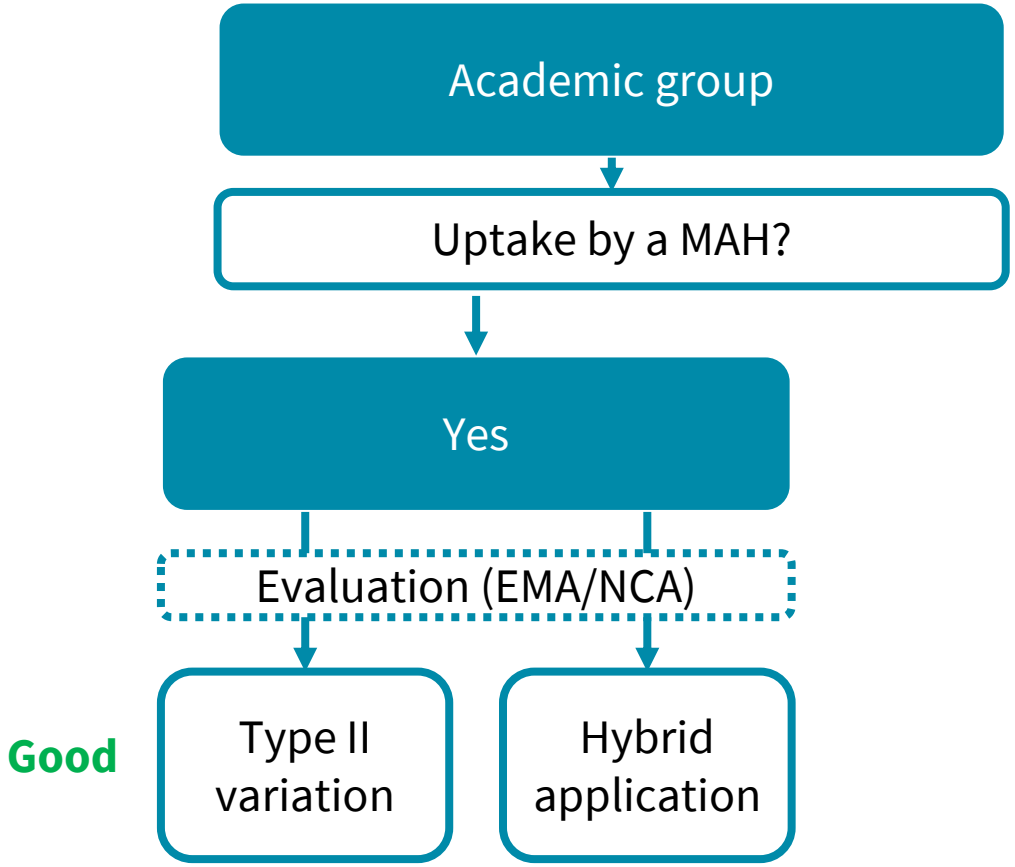




Matches the rarity of the disease → ultra-rare situation

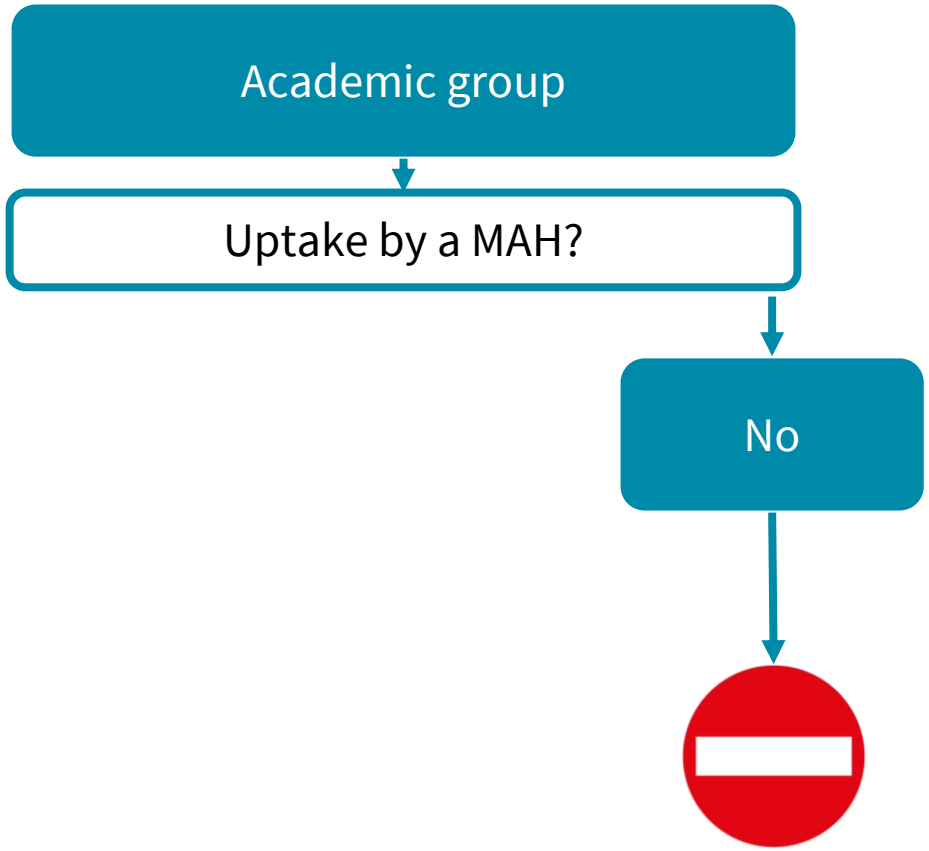

Repurposing of an authorised medicinal product
Main clinical data generated by?
Academic group
Uptake by a MAH?
Yes
No
Evaluation (EMA/NCA)
Type II variation
Hybrid application

Yes, uptake by a MAH



- Rare, even more so if
  - Product is generic
  - New indication is (ultra-)rare
- Examples (ultra-rare tumours)
  - Crizotinib for ALK+ inflammatory myofibroblastic tumours (US COG data) → type 2 variation at EMA
  - Atezolizumab for Alveolar Soft-Part Sarcoma (NCI data) → sNDA at FDA

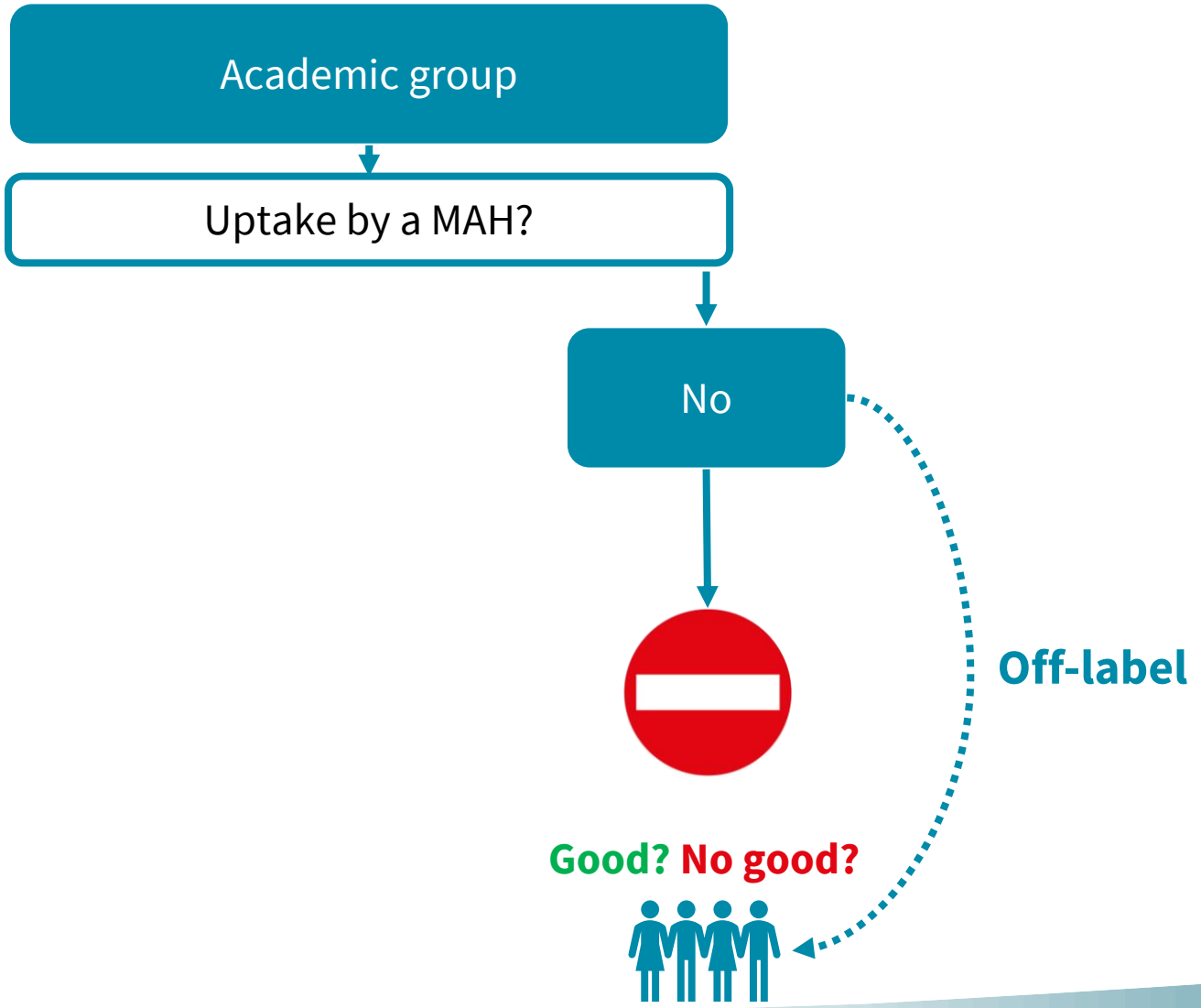
No uptake by a MAH



Good? No good?

- Frequent scenario
- Default when product is generic
- Examples (ultra-rare tumours)
  - Sirolimus for Epithelioid Haemangio-Endothelioma
  - Anti-PD-1 for Gestational Trophoblastic Neoplasia
  - Bortezomib for T-cell lymphoblastic lymphoma
  - Sunitinib for phaeochromocytoma and paraganglioma

No uptake by a MAH → off-label



3 timepoints to engage

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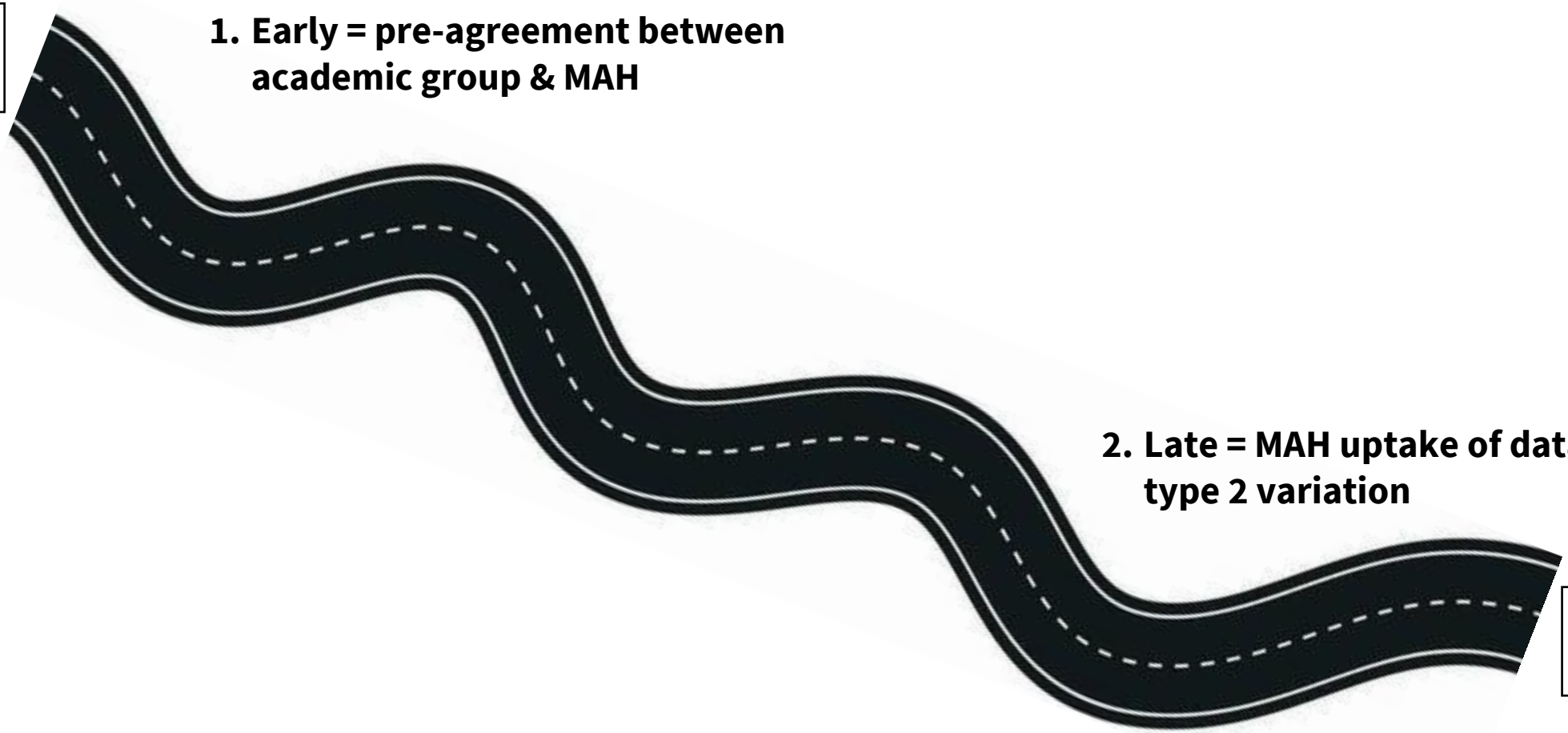
START (idea)

1. **Early = pre-agreement between academic group & MAH**

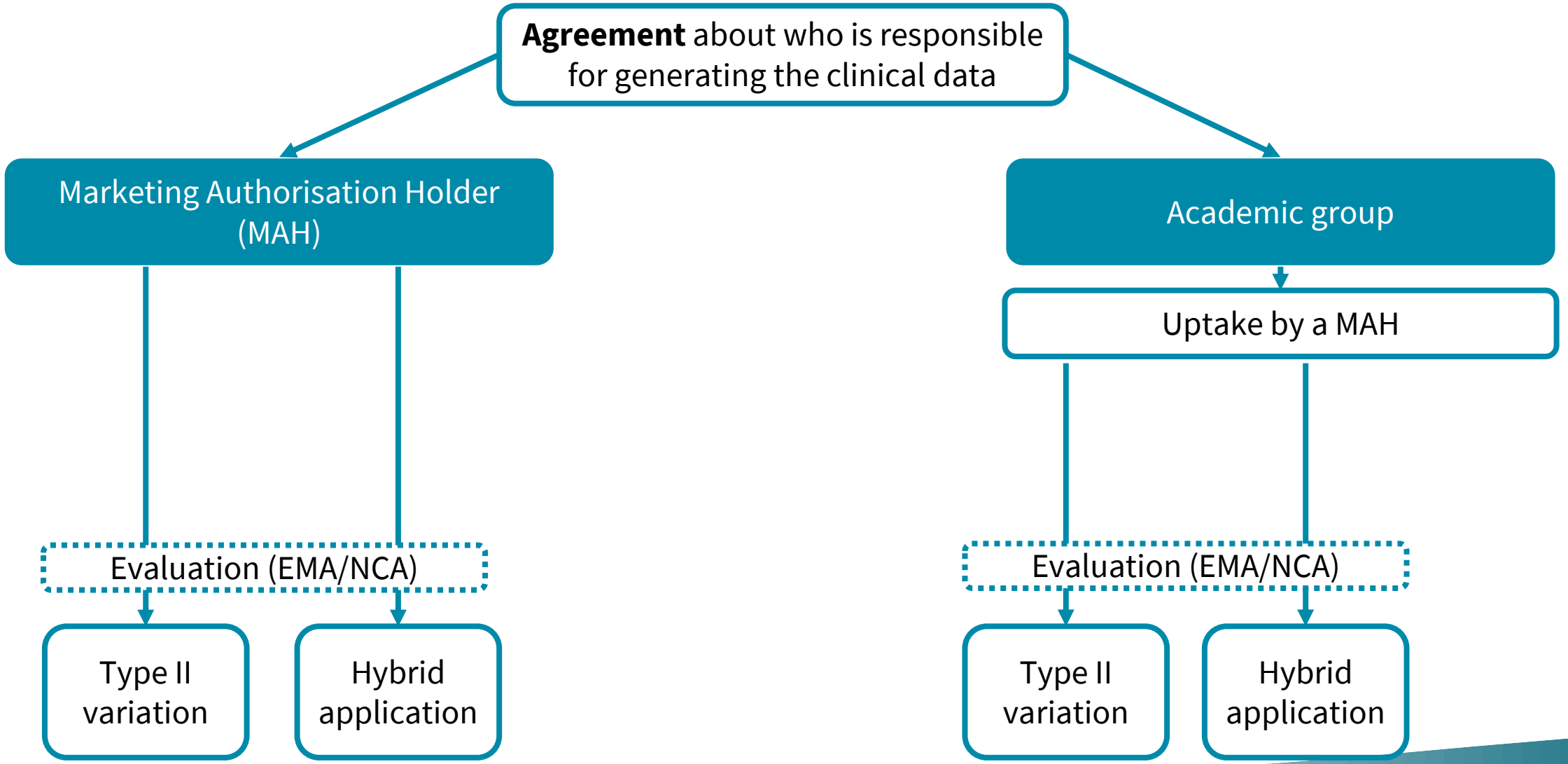


2. **Late = MAH uptake of data → type 2 variation**

FINISH (approval)

3. **Very late = EMA evaluation of data package (article 48)**

1- Early = Pre-agreement



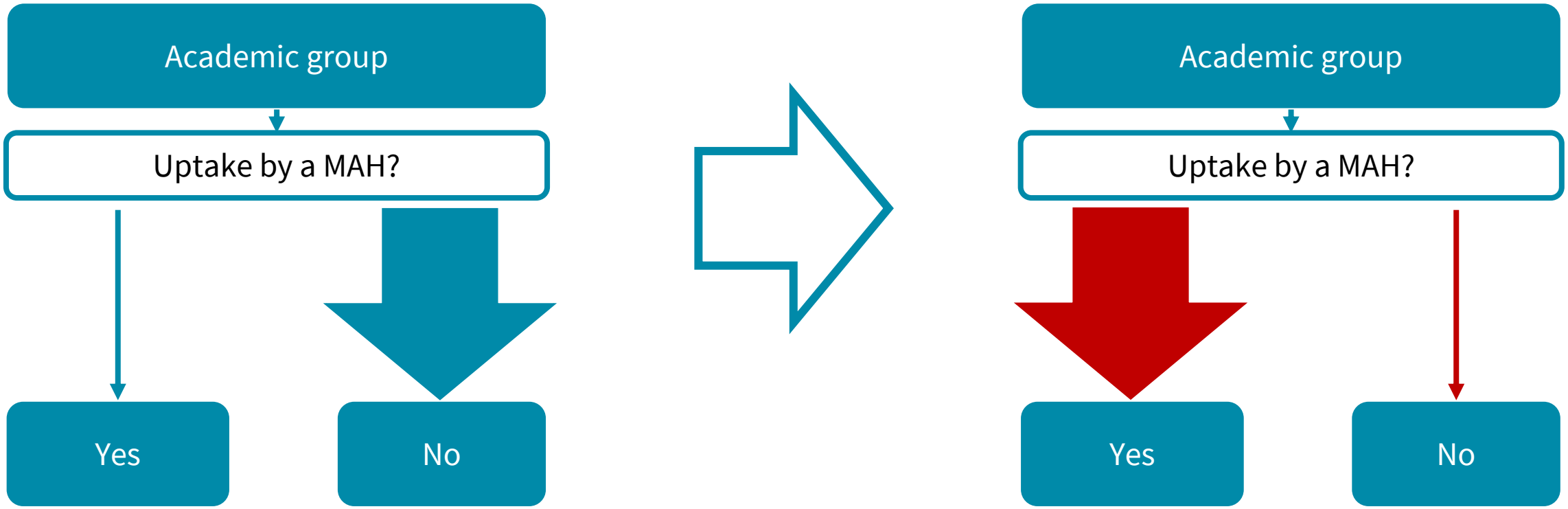
1- Early = Pre-agreement

- Examples
  - Alpelisib in PIK3CA-Related Overgrowth Syndrome→ development initiated by academics and then led by company
  - University College London and Astra-Zeneca (*Meade 2021 Contemp Clin Trials*)
    - UCL acting as trial sponsor. AZ providing funding and drugs.
    - Start-up agreement followed by full collaboration agreement
    - Joint pre-IND (FDA) and SA (EMA)
    - Agreement on protocol, data collection plan, operational aspects

1- Early = Pre-agreement

- **Strategic Forums**
  - Multiple stakeholders
  - Is it a good lead from a patient & science perspective?
  - If so, prioritise and make a plan
- **Streamline** trials for companies **(SARC, EORTC, PUSH)**
- **Role of trial funders** to promote/request pre-agreements

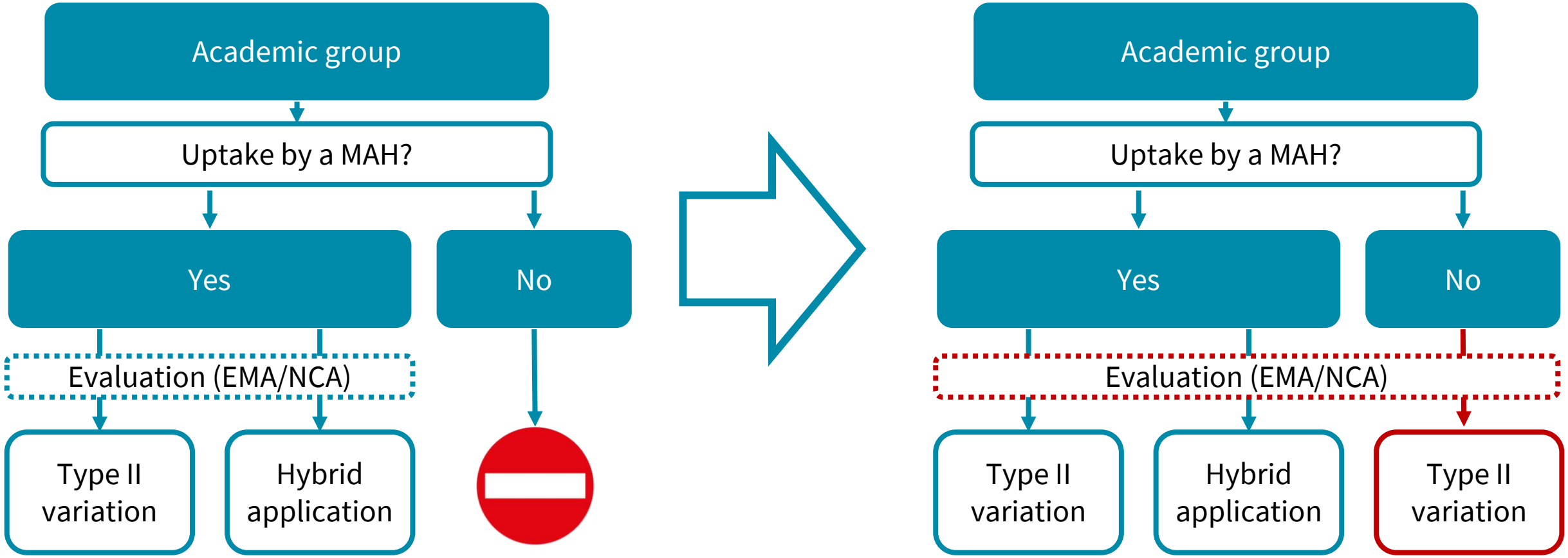
2- Late = uptake by MAH



2- Late = stimulating uptake by MAH

- **Direct incentives to MAH**
  - Financial: reward, prize, voucher, differential pricing & reimbursement ...
  - Lower upfront investment: simplification, reduced fees, support …
- **But other complex issues needs addressing** 
  - Due diligence & agreement with data owner
  - Liability
  - Potential loss: opportunity cost, mandated lowering of price …

3- Very late = EMA evaluation



Article 48

Final thoughts

- Patients & funders of academic trials – be demanding
- Academia
  - Ultimate goal should be approval – not fame or career advancement
  - Prioritisation, timing, collaboration & clarity about expectations
  - Get educated about regulation and drug development
- Companies
  - Corporate social responsibility to test drugs in rare cancers/populations
  - Help make data generated by academia good enough for submission

→ **Test the concept of UR tumours strategic forums?**