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RARE DISEASE AND ORPHAN DRUG DEVELOPMENT
EFFICIENT TRIAL DESIGN TO MINIMISE CASH BURN

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1. ORPHAN DRUGS : DEVELOPMENT PRINCIPLES

ORPHAN DRUG DEVELOPMENT PRINCIPLES

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Duties to	Purpose
Patients	• *Bringing the safe and effective therapeutic option in the **shortest time** to all patients and ensuring that the **risks are identified** and **adequately mitigated***
Investors	• *De-risk drug development in the **shortest time** through the most professional and efficient work to ensure the financial **risks are identified** and **adequately mitigated***
Regulators	• *Assurance to provide comprehensive, consistent and high quality data for appropriate review and opinion in the **shortest time to** ensure that the **review risks are identified** and **adequately mitigated***
Payers	• *Assuring "market access" in the **shortest time** and proposing a creative price model based on the demonstrated clinical benefit to ensure that the **commercial risks are identified** and **adequately mitigated***

ROAD TO THE FINAL OBJECTIVE

CASH BURN IS DIRECTLY LINKED TO TIME TO MARKET

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2. ORPHAN DRUG : REGULATORY WORLD

UNIQUE ASPECTS OF ORPHAN DRUG DEVELOPMENT

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Small population

- Limited opportunity for studies and replication in clinical trials
- Few treating physicians
- Few treatment centres

Clinical condition

- Serious and life-threatening
- High unmet medical need
- Lack of regulatory and development precedent

Multiple Collective Endpoints

- Efficacy markers selection
- Outcome assessment tools (often lacking)

Many rare and orphan diseases affect paediatric patients

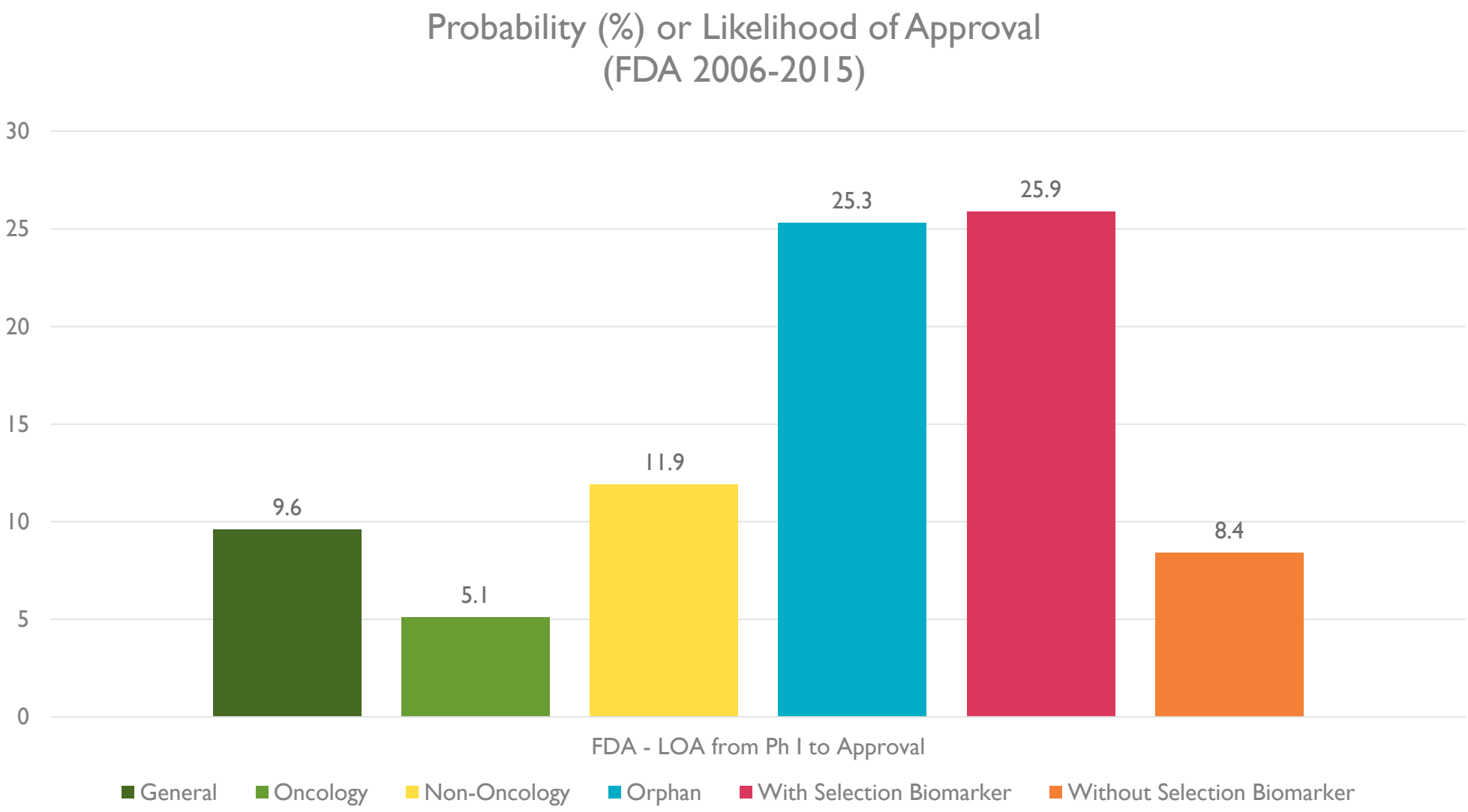
- Different PK / PD
- Dose modelling and simulation
- Visit/hospitalisation
- Ethical issues

REGULATORY CONDITIONS & REVIEW EU VERSUS USA

	EU	US
Legal Framework	EC/141/2000	Orphan Drugs Act 1983
Prevalence	5 in 10'000	≤ 200'000
Incentives	• Accelerated review schemes • 10 yrs ME + 2 years if paediatric	• Accelerated review schemes • 7 yrs ME
Time to ODD	90 ds COMP + 30 ds EC	No limits (1-3 mo)
Procedural	Centralised (EU)	FDA
Clinical Development Cost	(Single MS* tax credit)	Tax credit up to 50%
ODA/ODD Cost	Free	Free
Agency Support	Free SA and PA	Free OOPD Assistance
MAA	40% reduction fee or free for SME or paediatric	Fee Reduction
Public Funds	EC grants or single MS grants	Grants and Contracts

FDA /NDA or BLA	EMA
Priority Review	PRIME
Accelerated Approval	Accelerated Review
Fast Track	
Breakthrough Therapy	

FROM PHASE I TO APPROVAL



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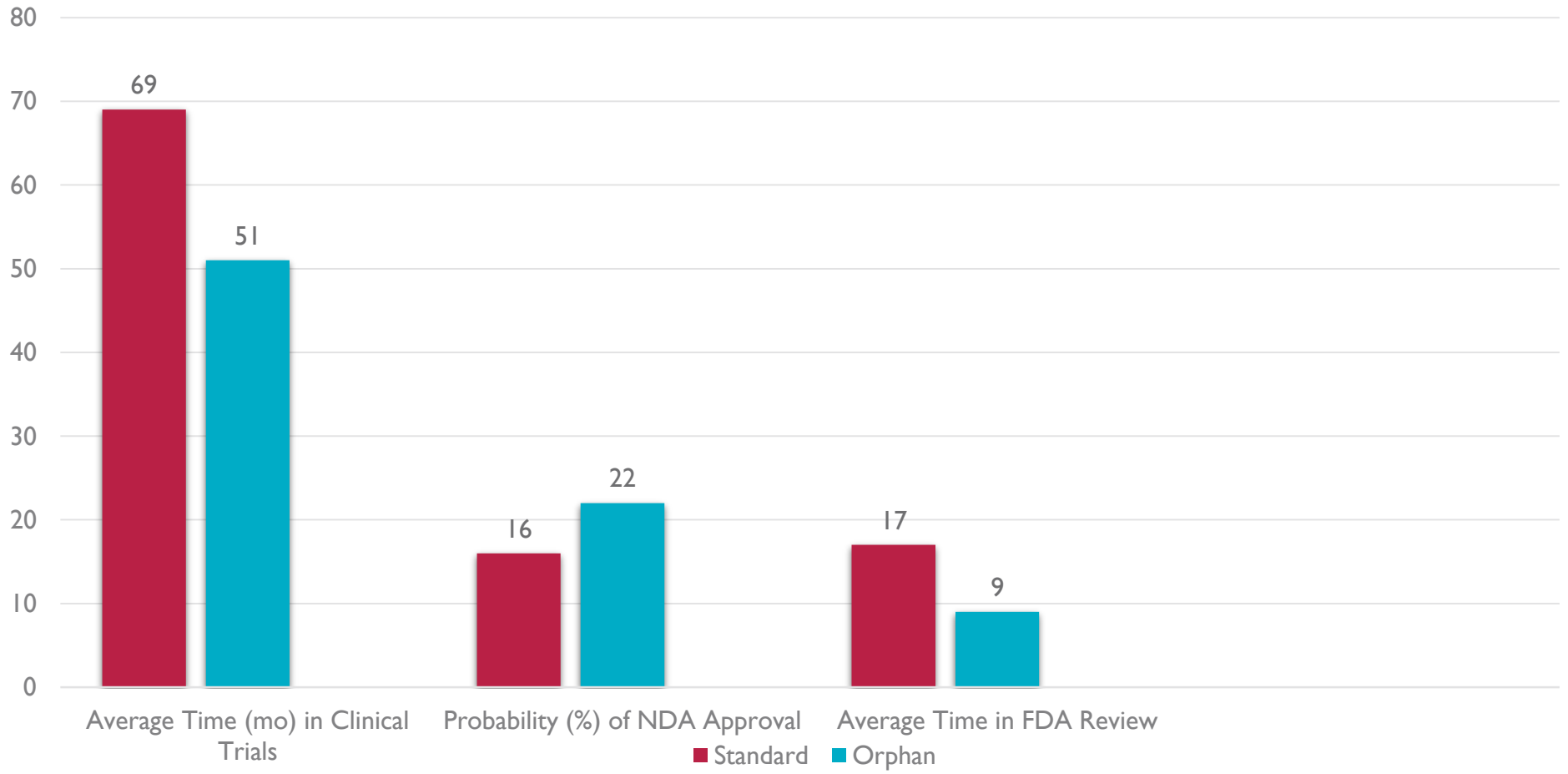
US Development Time Standard vs. Orphan Drugs



TRANSPARENCY IN THE REGULATORY PROCCESS

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POSITIVE EVOLUTION OF REGULATORY PATHWAYS IN THE EU AND THE US

MORE DETAILED AND SPECIFIC

REGULAR INTERACTION BETWEEN FDA AND EMA

MORE OPPORTUNITES TO INTERACT WITH FDA AND EMA

YOUR REGULATORY STRATEGY SHOULD INCLUDE FDA AND EMA

APPROVAL

ORPHAN DRUG DEVELOPMENT GIVES MARKET EXCLUSIVITY TO THE FIRST TO BE APPROVED

EARLY INTERACTION WITH THE AUTHORITIES= INCREASED PROBABILITY OF SUCCESS

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3. KEY CHALLENGES TO IMPROVE COST-EFFICIENCY IN CLINICAL DEVELOPMENT OF ORPHAN DRUGS

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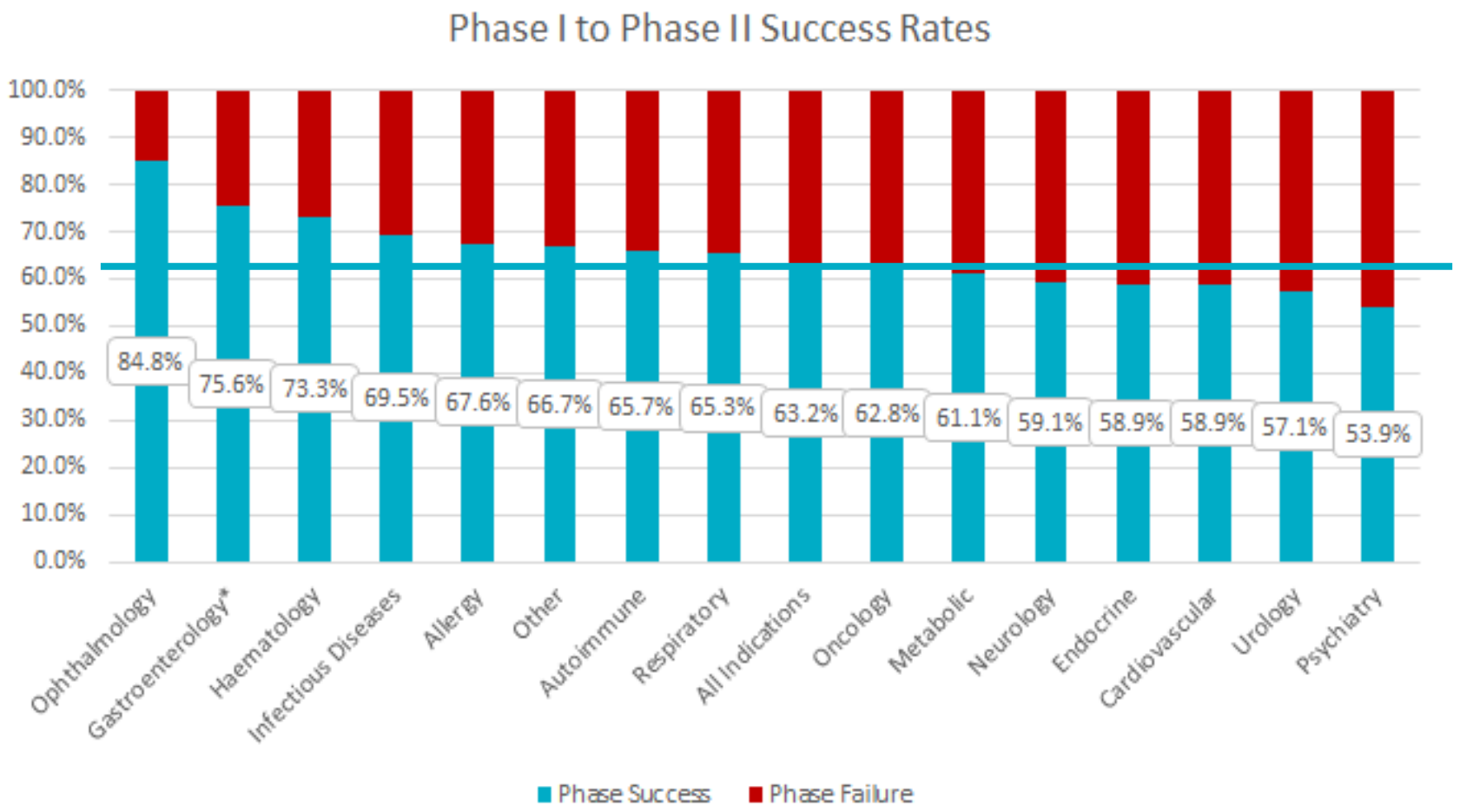
On average ~ 37% of drugs in Phase I don't move to Phase II



Data from Clinical Development Success Rates 2006-2015 produced by BIO, Biomedtracker & AMPLION

CONSIDER THE LOCATION OF YOUR PHASE I STUDIES

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UK has the probably strictest safety regulations in Phase I studies.

The MHRA is respected by the FDA & UK data accepted by them

Keep a dialogue open with FDA MHRA

In the USA

- For FiH studies in the US you must have the IND written before you enter the clinic
  - up to 6 months to prepare & submit

In the UK

- For FiH studies in the UK you need a CTA only before you enter the clinic
  - 2 months to prepare & submit.

Without the initial need for expensive IND, in the UK you can have data coming back from the clinic before you've even started enrolling volunteers in the USA.

If your data is positive, then apply for the IND

REDUCED FINANCIAL RISK, REDUCED TIME, INCREASED SPEED TO PATIENTS.

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TRANSLATIONAL EXERCISE

TRANSLATIONAL EXERCISE

- Accurate animal model (reproducible disease)
- Outcome of reliable research (PK, PD) and toxicity data
- **Dose modelling and simulation**
- Comprehensive information of the natural history
- Translation of markers non-clinical into clinical
- **Development of meaningful markers: clinical, biological and imaging**
- **Validation of selected markers**
- **Development of accurate tools to evaluate safety and response to the treatment**
- Useful drug product pharmaceutical form and route of administration
- **Identification of patient selection Markers, Biomarkers and / or Molecular markers**

- ✓ Dose selection
- ✓ Safety: risk and minimisation
- ✓ Selection of efficacy endpoint
- ✓ Selection of primary and secondary endpoints
- ✓ Patient stratification upon "selection biomarkers"
- ✓ Selection of meaningful disease evaluation tools

"… The time invested in consistent non-clinical and toxicity studies and …

… the validation of assays…

… reduce the risk of failure in the clinical development and increase the certainty of clinical pathway…"

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CLINICAL STUDY DESIGN

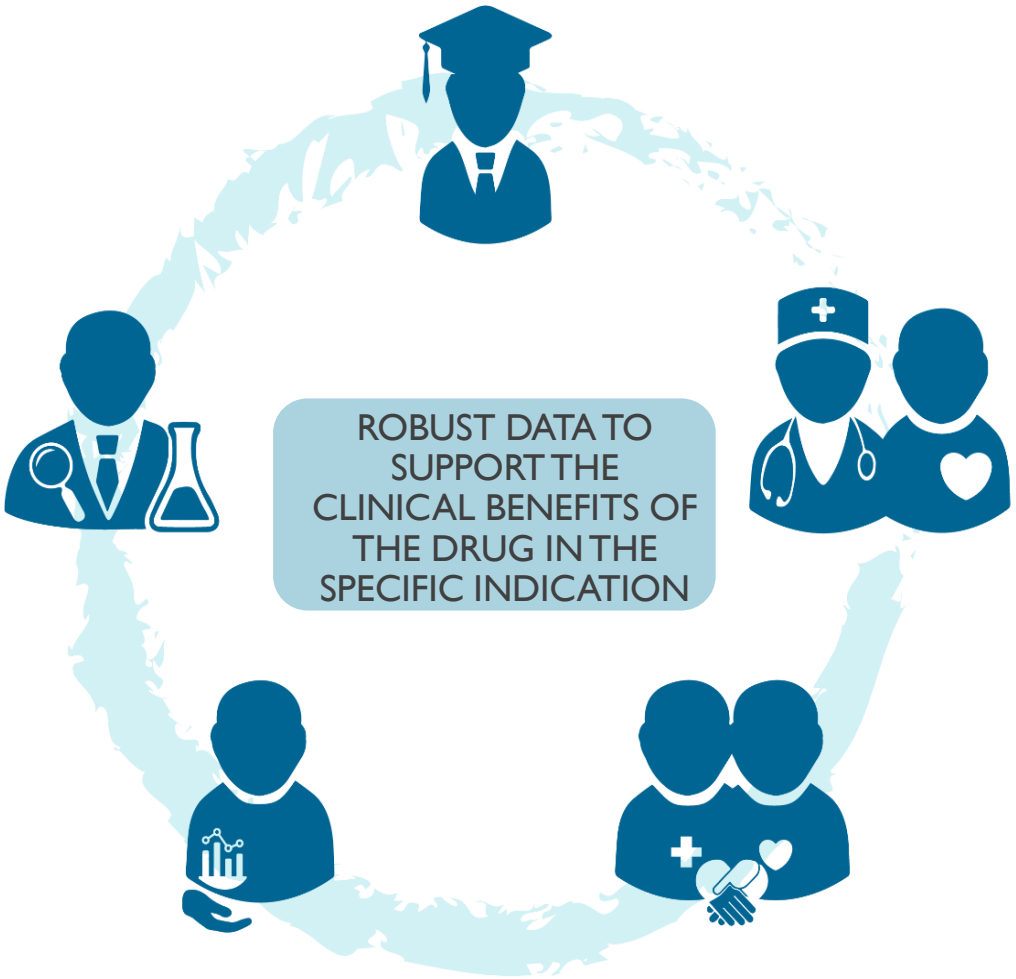
"Clinical development must deliver payer value…

… focusing on primary and secondary endpoints …

… deliver value to the healthcare system …

… deliver true benefit…"

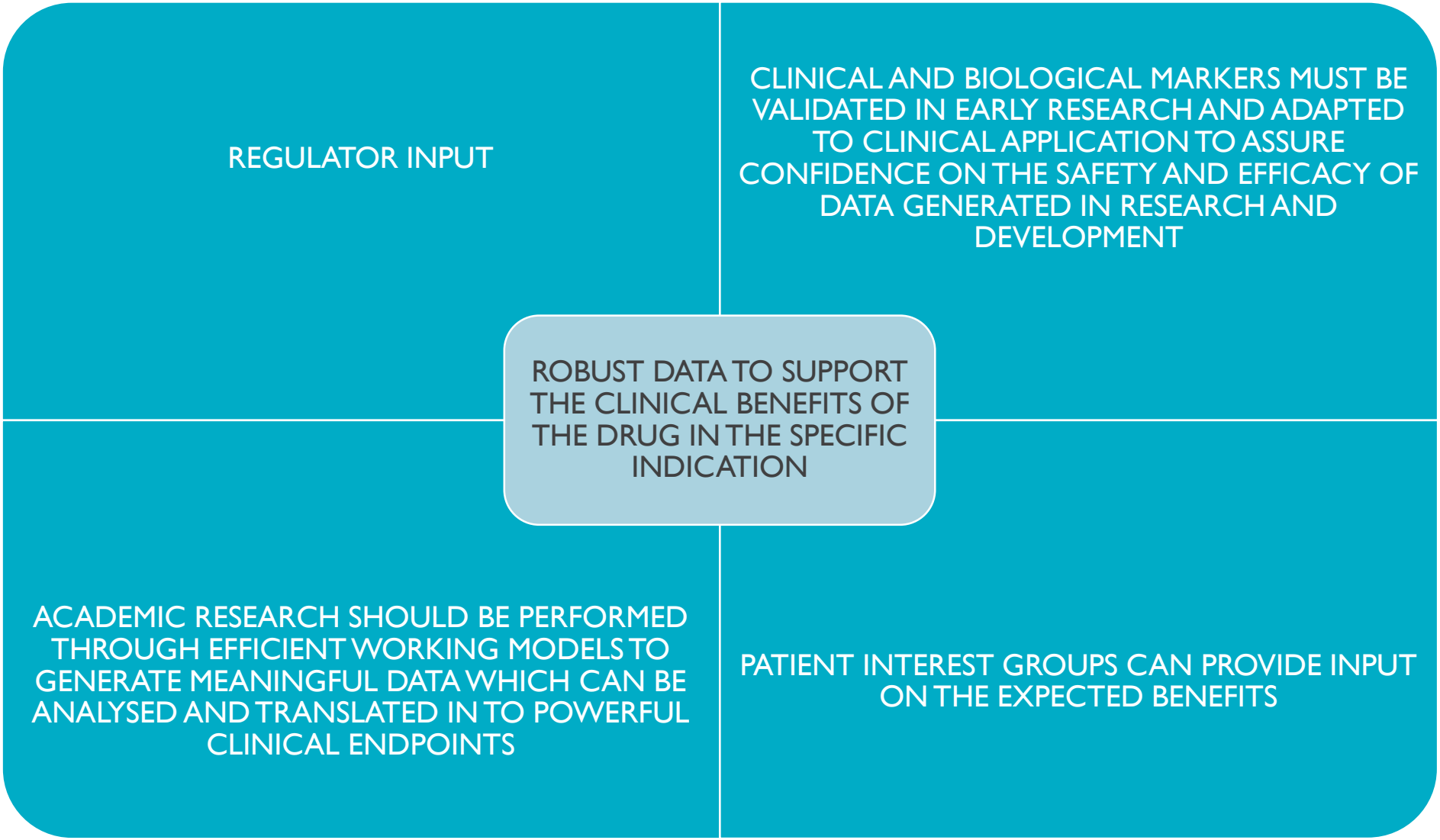
THE IMPORTANCE OF MULTI-STAKEHOLDER COLLABORATION



Multi-disciplinary research and development consortium

- Academic researchers
- Clinical experts
- Patient associations
- Statisticians
- Drug developers
- Government research (NIH)

MULTI -STAKEHOLDER COLLABORATION



STUDY DESIGN CONSIDERATIONS

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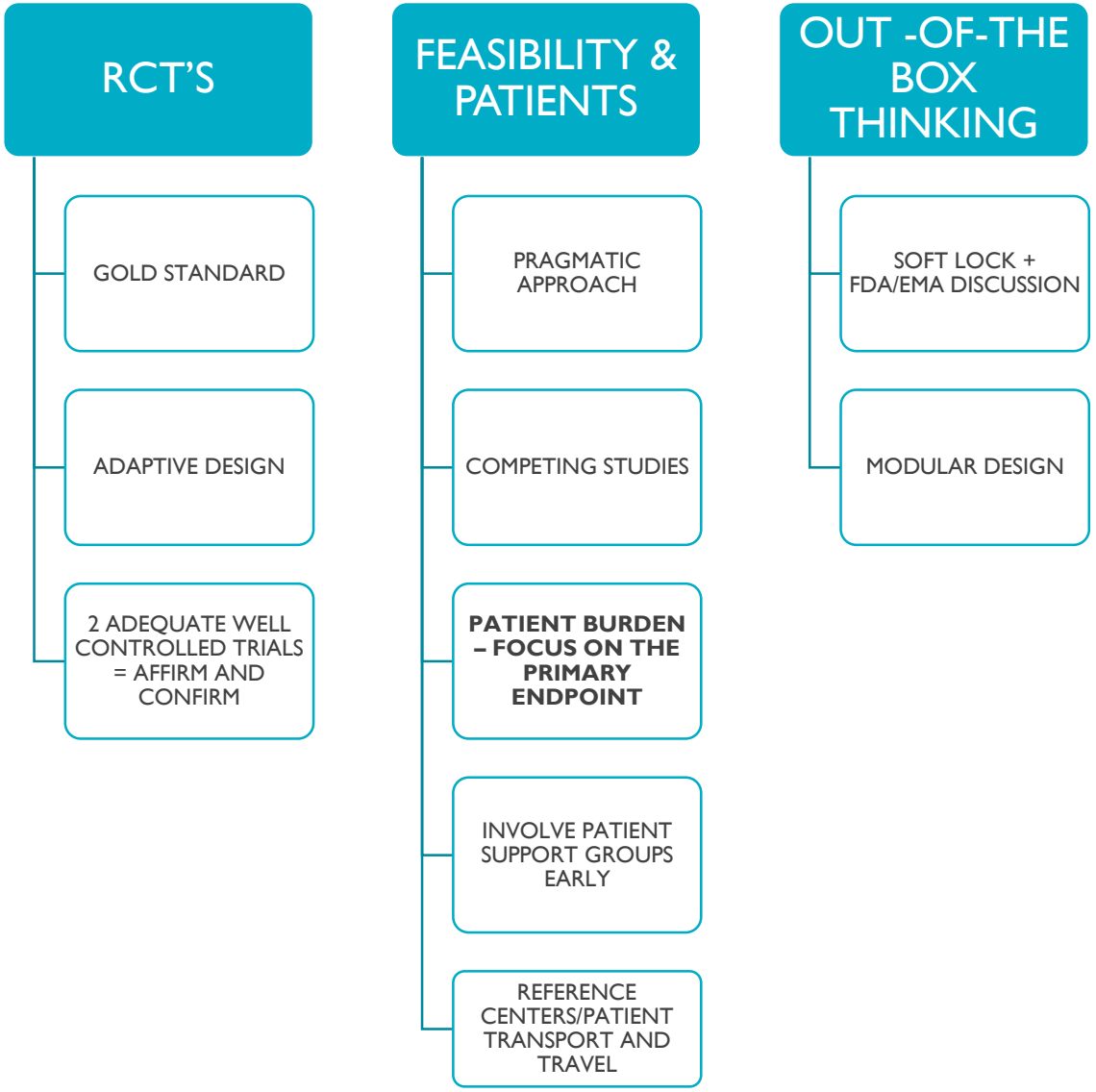

PROTOCOL DESIGN – SOME IDEAS

Historical cohort as control group / Natural history

Patient Input

Observational or interventional non-therapeutic protocol to enrol patients into a study - with a therapeutic roll-over protocol

Deviating from regulatory guidelines does not mean that we do not know the guidelines.

It is because there is a strong rationale to do so.

The more we deviate from guidelines the more we have to demonstrate to the regulator that we are fully aware of those guidelines.

Ask for a meeting with regulatory bodies: FDA, EMA, MHRA

The clinical development plan should be creative enough to design the base endpoints to facilitate the regulatory review and approval processes, with follow-up post marketing surveillance to fill-in any 'gaps' and bring confidence of a smooth and successful market access.

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SITE & COUNTRY SELECTION

SITE SELECTION AND MANAGEMENT

- ✓ Engage in a partnership with sites early
- ✓ Site specific approach, recruitment strategies and Site Management Plan
- ✓ Flexibility in SOPs and logistic processes "hand made" vs "mass produced"
- ✓ Involve reference centres
- ✓ Organising patients' transport is a much lower cost than opening new countries and sites
- ✓ Quality and integrity of data critical in view of the low volume
- ✓ Secure the primary endpoint
- ✓ Limit academic approach to avoid unnecessary tests

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PATIENT RECRUITMENT AND RETENTION

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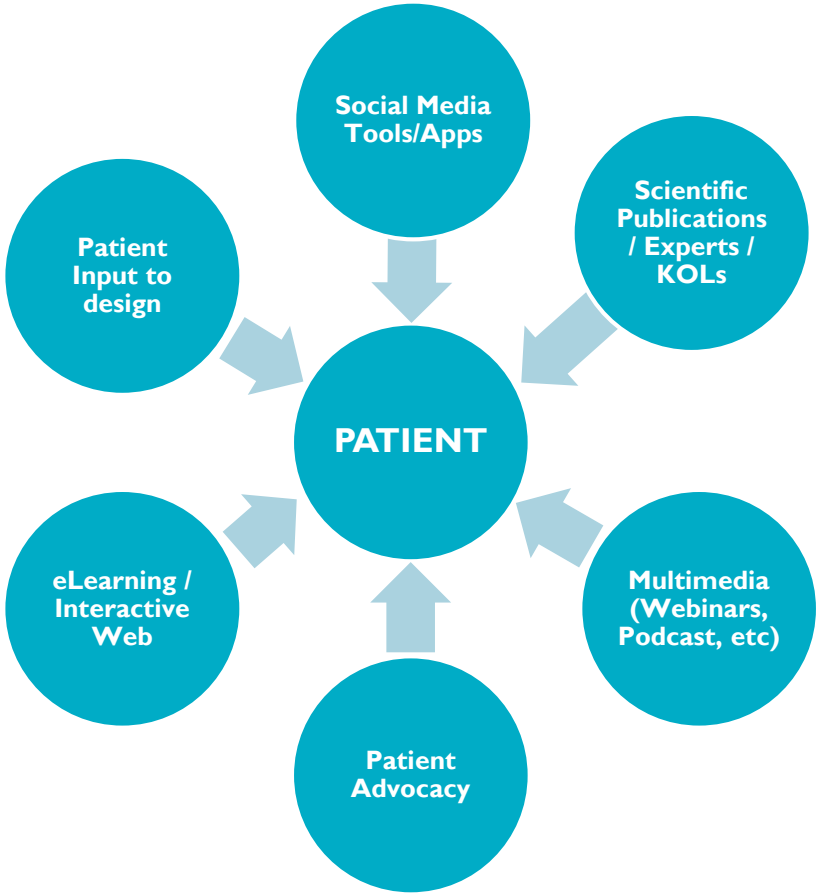
Early patient engagement leads to deeper insights into the high unmet need and the potential impact the asset would have on alleviating symptoms and improving quality of life



APPROPRIATE PATIENTS

Identifying the **appropriate patient** is defining and identifying those patients most likely to be responders.

- Numbers needed to treat (NNT)
- Disease progression
- Proper diagnosis
- Biological markers
- Imaging markers

RECRUIT, RETAIN, REPORT

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RECRUIT

- Finding the right patients for a rare disease clinical trial could be a real challenge for acute conditions'
- No predictive recruitment model for acute conditions
- Active pre-screening campaign for chronic disease
- The % of the patient population to screen could be close to 100% for some conditions

RETAIN

- Each patient becomes a "Project" in itself
- Send reminders for upcoming visits
- Provide a comfortable, friendly environment
- Accommodate to their schedule as much as possible
- Perform patient visit simulation

REPORT

- Across all Clinical Trials
  - 85% of clinical trials fail to retain enough patients
  - Average dropout is 30%
  - Main reasons for drop-out includes financial constraints to being physically unable

ELEMENTS OF STUDY MANAGEMENT

- Flexibility - Sites / Countries / Recruitment Strategies / Reference Centres – transporting patient is cheaper than opening countries and sites
- Small / medium size CROs – more dedicated and personalised / partnership
- Vendor management
- Advisory board
- Limit academic approach
- Paper CRF could be used, if very small cohort
- Endpoint showing medical/clinical benefit
- Quality of data
- Focus on the patient
- Payment schedule
- Rationalise the use of central laboratory
- Secure the primary endpoint
- Reduce the size of your project team (ultra specialised) increases efficiency
- Website for patient communication
- Patient associations
- Soft lock/interim report
- Investigator meetings need to be perfectly organised
- Regular TCs with the sites

MITIGATING CASH BURN SUMMARY

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Apply more rigor and discipline to the research and development processes avoiding shortcuts such as truncated Phase I or Phase II studies and inadequate understanding of regulatory requirements

Understand critical components in earlier development phases in order to reduce later-stage failures

Apply more disciplined protocol review and optimization as well as use of modelling and simulation, adaptive trial designs and biomarkers

Mitigate study execution risks. It should leverage data from a variety of sources and conduct ongoing surveillance of the quality of data being collected, while tying this to a risk-based monitoring protocol

Ensure completeness and clarity of submissions for regulatory agencies. Seeking advice from regulators during the drug development process in order to discuss the plan and identify areas of concern requiring adjustment

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