Rare Disease Clinical Trials

An Opportunity for Differentiated Services

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WORLDWIDE CLINICAL TRIALS

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Agenda

Redefining the Method

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Redefining the Art

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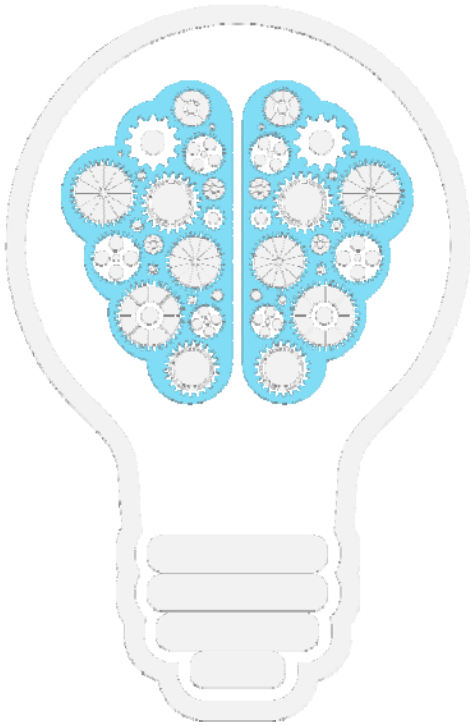

POLL #1

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Rare Disease Clinical Trials: An Opportunity for Differentiated Services

Redefining the Method

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What Are They?

- Acromegaly
- Amyotrophic Lateral Sclerosis
- behavioral variant, Frontotemporal Dementia, Granulin mutation
- Bullous pemphigoid
- Cystic fibrosis
- Duchenne muscular dystrophy
- Down Syndrome
- Fabry disease
- Gaucher disease
- Growth hormone insensitivity syndrome (Laron Syndrome)
- Hemophagocytic lymphohistiocytosis
- Idiopathic pulmonary fibrosis
- Idiopathic thrombocytopenic purpura
- Juvenile idiopathic arthritis
- Lambert Eaton myasthenic syndrome
- Mucopolysaccharidosis I (Hurler syndrome)
- Mucopolysaccharidosis II (Hunter syndrome)
- Mucopolysaccharidosis VI (Maroteaux-Lamy syndrome)
- Niemann–Pick type C
- Pulmonary arterial hypertension (PAH)
- Sickle cell disease
- Hemophilia B
- Thrombotic microangiopathy: Thrombotic thrombocytopenic purpura (TTP)
- Von Willebrand disease
- Velocardiofacial syndrome, psychosis

What is an orphan indication?

- US = Fewer than 200,000
- Europe = 1/2000
- “Ultra” adds an additional dimension
- Genotypic- phenotypic variation
- Frequently multiple organ systems affected
- Coordinated multidisciplinary care
- Frequent transition points in clinical care
- Collectively, 7,000 diseases affecting 300 million people worldwide

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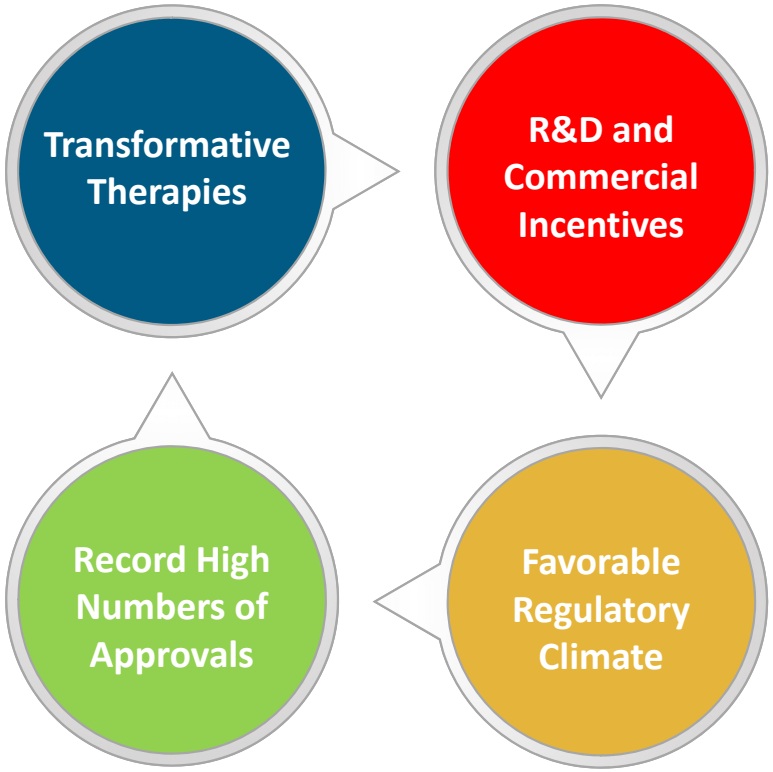
… With an Opportunity to Apply Innovation

- Permissive science, innovative technology
- Novel and repurposed products
- Evolving regulatory climate
- Innovative, efficient study designs
- Diverse Measures
- Unique operational solutions
- Participatory research models
- Globalization in clinical research



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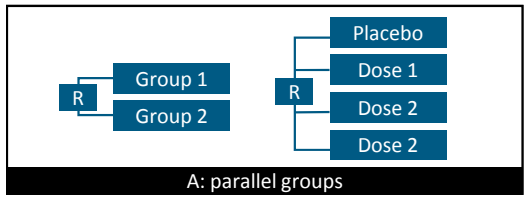
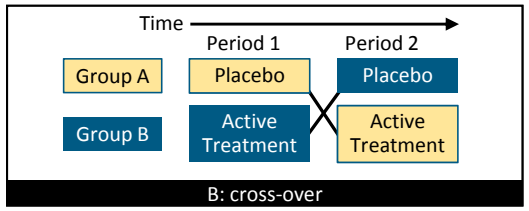
http://www.21stcentech.com/genomics-key-defeating-orphan-diseases/

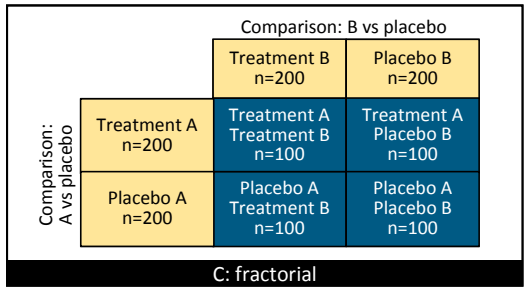
Creative Designs for Interventional Studies



A: parallel groups



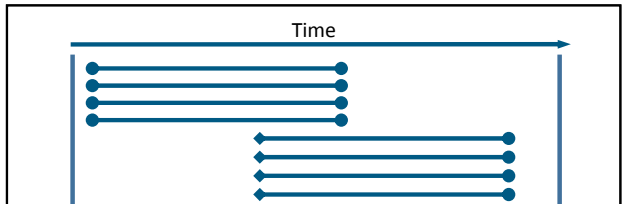
B: cross-over



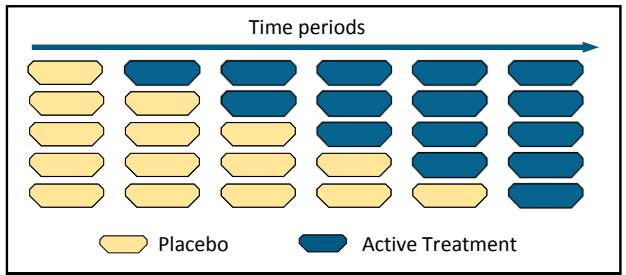
C: fractorial

Period 1	Period 2	Period 3	Period 4	Period 5	Period 6
A	B	B	A	A	B
Sequence 1		Sequence 2		Sequence 3	

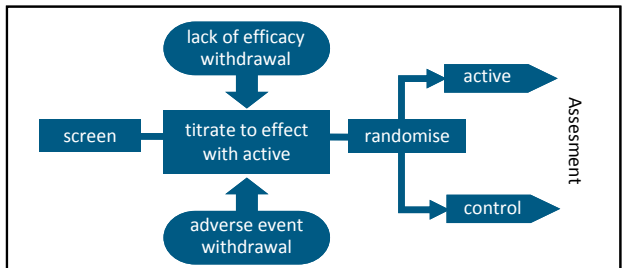
D: N-of-1



E: randomised placebo phase



F: stepped wedge



G: randomised withdrawal

See Cornu et al, 2013; Gagne et al 2014

Minimizing sample

- Adaptive randomization
- Longer trials, more events/ patient
- Risk stratification
- Continuous and composite measures,
- “relaxed alpha’s”
- Bayesian frameworks

Maximizing treatment

- Imbalanced randomization
- Crossovers and permutations
- Factorial
- “n-of-one”
- Randomized placebo
- Stepped wedge and variations
- Randomized withdrawal

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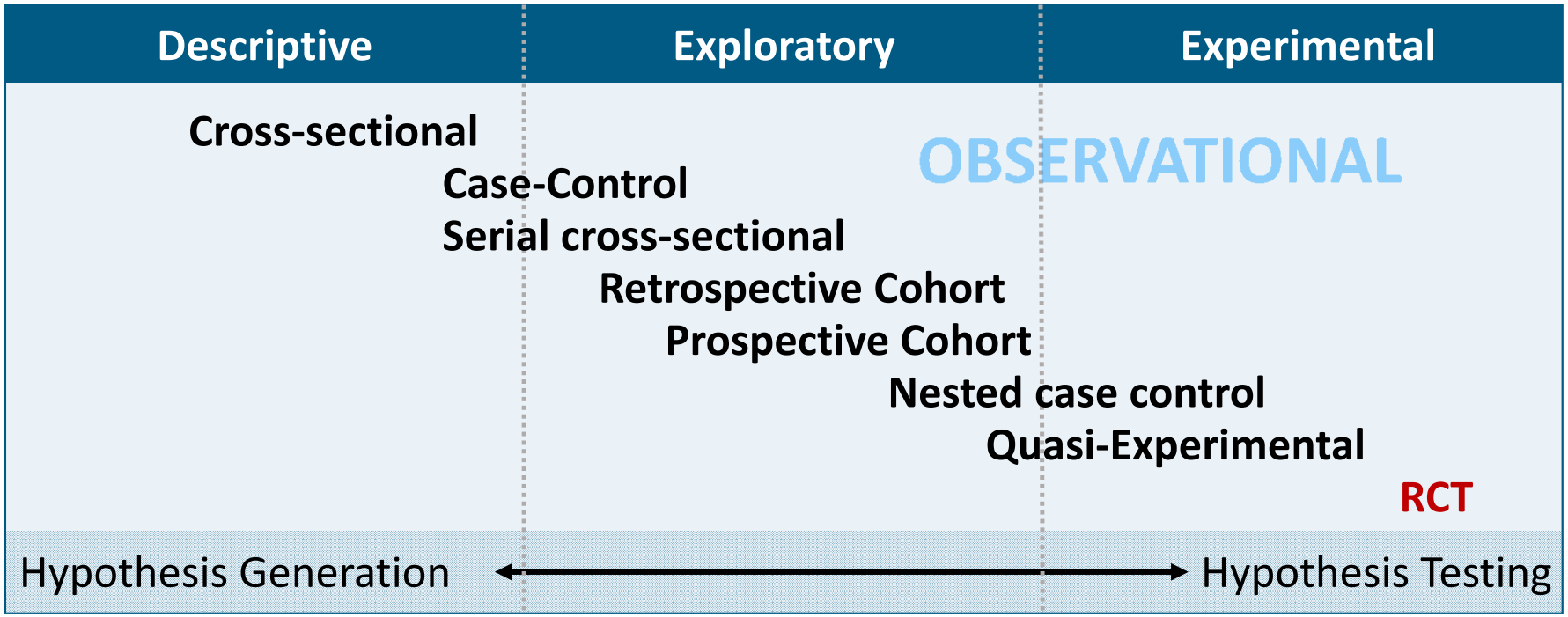
… With a Portfolio of Observational Options



Shah, N. Evidence standards in the era of comparative effectiveness. AHDB.2(1): s41-s48, 2009.

…That Can Answer Diverse Questions

To inform protocol design?

As a complement to a submission strategy?

To shape formulary & reimbursement decisions?

With many objectives

- Natural history of disease
- Burden of illness
- Treatment Pathways
- Disease Management
- Post-Marketing Usage (on & off label)
- Comparative effectiveness

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… Noting Every Orphan is Uniquely Different

Behavioral Variant, Frontotemporal Dementia, Granulin Mutation
"medical monitor as an internal CMO"

Gaucher Disease
"design and operations are always linked"

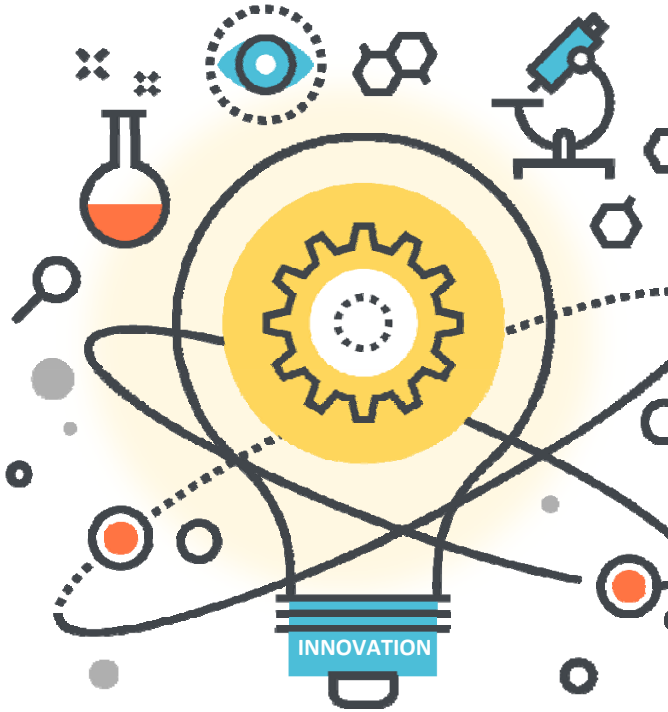
Pulmonary Arterial Hypertension (PAH)
"everyone wants the same patients"

Thrombotic Microangiopathy: Thrombotic Thrombocytopenic Purpura (TTP)
"sometimes there is rare, and then there's really rare"

Hemophagocytic Lymphohistiocytosis
"multinational studies, multilingual complex informed consents"

Defining The Box, Then Stepping Out Of It

- The conundrum of placebo?
- The contribution of historical data?
- Most sensitive and specific measures in a multi-organ disease state?
- Innovative designs?
- Hybrid monitoring strategies?
- Is a “one and done” registration strategy tenable?



Evidentiary Standards - Orphan Drug Approvals

	Brand Name (Chemical Name)	Approval (mo/y)	Type of Efficacy Evidence: Conventional	Administrative Flexibility	Case-by-Case Flexibility
1	Abthrax (raxibacumab)[b]	12/2012		✓	
2	Adempas (riociguat)	10/2013	✓		
3	Anascorp (centruroides scorpion antivenom)[a]	08/2011		✓	
4	BAT (botulism antitoxin hepavalent)[b]	03/2013		✓	
5	Corifact (coagulation factor XIII concentrate [human])[a,b]	02/2011		✓	
6	Elelyso (taliglucerase alfa)[a]	05/2012		✓	
7	Ferriprox (deferiprone)[b]	10/2011		✓	
8	Firazyr (icatibant)[a]	08/2011		✓	
9	Gattex (teduglutide [rDNA origin])[a]	12/2012		✓	
10	Hetlioz (tasimelteon)	01/2014	✓		
11	Impavido (miltefosine)[a]	03/2014		✓	
12	Jakafi (ruxolitinib)	11/2011	✓		
13	Juxtapid (lomitapide)	12/2012			✓
14	Kalydeco (ivacaftor)	01/2012	✓		
15	Kcentra (prothrombin complex concentrate [human])	04/2013	✓		
16	Krystexxa (pegloticase)	09/2010	✓		
17	Kynamro (mipomersen)[a]	01/2013		✓	
18	Makena (hydroxyprogesterone caproate)[a,b]	02/2011		✓	
19	Myalept (metreleptin)	02/2014			✓
20	Northera (droxidopa)[b]	02/2014		✓	
21	Nulojix (belatacept)	06/2011	✓		
22	Onfi (clobazam)	10/2011	✓		
23	Opsumit (macitentan)[a]	10/2013		✓	
24	Signifor (pasireotide diaspartate)	12/2012			✓
25	Sirturo (bedaquiline)[b]	12/2012		✓	
26	Vimizim (elosulfase alfa)	02/2014			✓
27	Voraxaze (glucarpidase)	01/2012			✓
	Subtotal		8	14	5
	Total		8	19	

[a]Single-study approval authority (May 1998 Evidence Guidance, FDAMA 115).
[b]Accelerated approval/Subpart H/Fast Track.

Conventional: at least two adequate and well-controlled trials, each meeting primary endpoint, by pre-specified primary analysis, $P \leq 0.050$

Administrative: two different methods, either affecting number of studies (e.g., single study) or type of evidence (subpart H).

Case-by-case

"…19, or just over two-thirds, of the 27 non-cancer orphan drugs approved between July 1, 2010, and June 30, 2014, were-based on some exercise of flexibility by FDA…"

Sasinowski FJ, Panico EB, Valentine JE. Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Update, July 2010 to June 2014. Therapeutic Innovation & Regulatory Science. 2015, 49(5): 680-697.

A Strategy for "One-and-Done" Programs?

"Accelerated"-"Fast Track"-"Breakthrough"

"[t]here is ***no specific minimum number of patients*** that should be studied to establish effectiveness and safety of a treatment for any rare disease." (Guidance for Industry - Rare (b) (6) (b) (6)(b) (6)Diseases: Common Issues in Drug Development, August 2015).

"*fewer, smaller, or shorter* clinical trials than is typical for a traditional approval…" ((FDASIA Section 901(a)(1)(C))

"trials using ***external controls, such as historically controlled trials*****,** may be considered adequate and well-controlled, and may provide or contribute to evidence of efficacy to support approval." (FDA Guidance for Industry: Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment, June 2015)

Explore

- Given that primary outcome is significant; secondary measures are supportive and GCP compliance assured

Is this true?

- "Informative" study already exists?
- Registry with case-controlled matching contributes to evidence of efficacy to support approval [e.g. Illustrated by Cole et al, 2011 for Gaucher Disease)?
- Prior clinical data & Post-marketing commitment to registry will support safety labelling?

But What if One Isn't Enough?

Issues :

- Proposed surrogate endpoint ≠ a clinical endpoint
- No surprise-> population too heterogeneous to find differences
- Possibly predictable-> therapies dangerous in combinations
- Patient population drifted -> risk and response different
- "The Will Rogers Effect"

Conclusions:

- Not TA specific--Divergent results across all indications
- Not MOA specific--Across classes of investigational products
- Limited data -- > limited utility of benefit : risk assessment

… In the Case of Uncertainty– “Go Registry”?

Risk Mitigation in Therapy

The Rise of Registries

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Identifying risk has consistently remained a top priority in clinical trials – especially in transformative therapies. With changes to study development, safety, value and innovation, the widespread utilisation of registries could mean a transformational shift across the whole trial landscape

Dr Paola Antonini, Lorna Graham and Dr Michael Murphy at Worldwide Clinical Trials

A range of novel scientific approaches to address various disease targets have characteristics associated with 'transformative therapies' – namely therapeutic interventions, which shift the objective of care from management of symptoms to control of disease through a modification of disease processes. Broad catagories of scientific platforms exist under this umbrella, such as cell therapy (induced pluripotent stem cells, direct reprogramming of differentiated cells), a variety of small molecules within different chemical classes, antisense RNA interference therapy, monoclonal antibodies and gene therapy.

Transformative Therapies

Although a variety of clinical development programmes can be characterised by investigational compounds meeting transformative definitions, the higher number of potentially breakthrough products in cancer reflects the growing understanding of disease processes at the molecular level. This includes insights gained through compounds investigated for multiple cancers that have similar underlying molecular mechanisms, but which may affect different organ systems.

Correspondingly, immunological conditions also share common pathophysiological touch points in spite of discrepancies in clinical expression, so potential therapeutic agents may be effective across multiple indications. As an example, there are more than 20 therapeutic monoclonal antibodies – either approved or in various stages of clinical development – that target molecular components of the cytokine cascades mediating inflammation (1). These diverse agents may interrupt pathways essential to the pathobiology of allergic asthma, inflammatory bowel disease (2), Crohn's disease (transmural inflammation) and ulcerative colitis (mucosal inflammation).

Implications for Clinical Development

The translation of molecular discoveries in the laboratory into novel clinical research and healthcare delivery mechanisms drives the development of clinical trial methodology. Innovative study designs adaptively evaluate unique product attributes, while accommodating patient subtypes and simultaneously building a longitudinal model of the disease process, which has clinical care implications (3). For instance, agents that affect nodal points in pathophysiology may be targeted across clinical conditions, which have different clinical expressions in an early clinical development strategy exploiting 'therapeutic adjacencies'.

In this stratagem – which continues discovery into development – an evaluation of pharmacological properties is pursued, using a common, existing target across multiple indications before committing to a clinical indication. Clinical research activity is predicated under an assumption that successful target engagement in one disease state may be transferable into another. However, as these agents can also have a locus of action upstream from the ultimate clinical presentation, there is a potential for introducing unanticipated adverse effects detected only with longer-term therapy in a more heterogeneous population. Given this potential, the contribution of registries to clarify treatment effects in representative populations – in the hands of representative physicians and over longer durations of exposures – is key.

Long-Term Safety

With transformative therapies, there is a need for long-term follow-up to identify risk, as well as value and benefits. These benefits can be seen as increased quality of life, prolongation of life (compatible with reasonable quality of life), and cost benefits based upon overall reductions in healthcare utilisation. This last attribute allows healthcare providers to facilitate access to expensive therapies without reducing provision for other healthcare needs, and to decrease the burden of illness from both a patient and social level.

Historically, registries have been associated with risk identification methods in relevant clinical settings.

Antonini, Graham, and Murphy, Worldwide Clinical Trials

Characterized

- Representative populations, representative providers
- Examination of “Interaction” effects
- Heterogeneous patient groups and disease trajectories

Objectives

- To inform *safety*
- To inform *value*
- To inform *future trials*
- To support *registration*?

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POLL #2

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Leslie Wetherell

Executive Director, Rare Disease Franchise

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Rare Disease Clinical Trials: An Opportunity for Differentiated Services

Redefining the Art

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POLL #3

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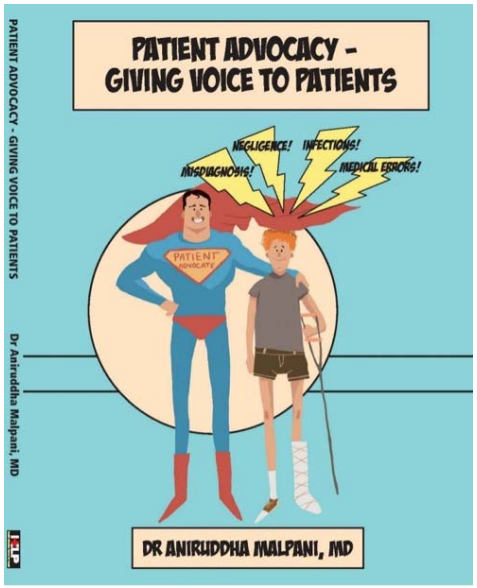
Patient Focused Engagement

- Patients and families provide insight into the “illness” vs. the “disease”
- Patients can help define robust patient engagement strategy
- Fitting patients’ life into trials doesn’t work as well as fitting trial into patients’ lives
- Patient voice should be routinely solicited to ensure outcomes that matter most to patients are met
- Not all risks are equally accepted and not all benefits are equally valued



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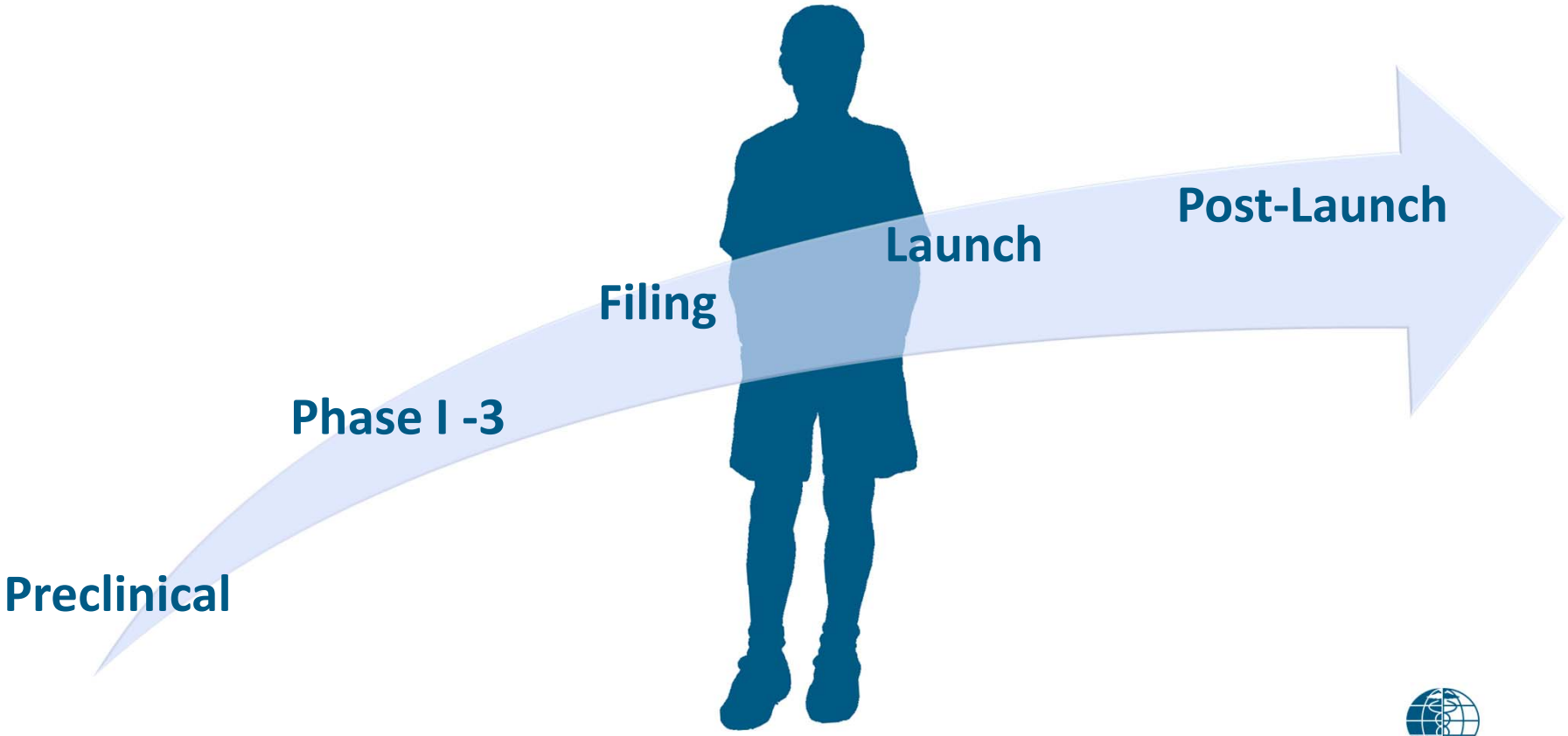
Patient Voice Throughout the Life of Trials and Beyond



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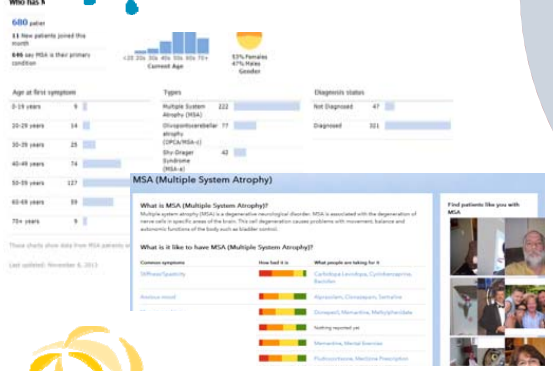
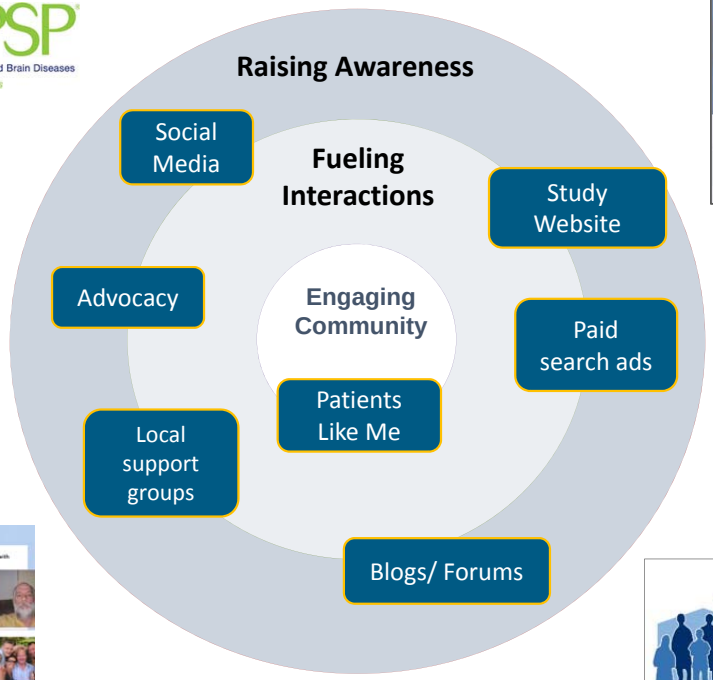
Outreach, Support and Engagement Tactics

RareConnect.org
A PARTNERSHIP OF EURORDIS AND NORD

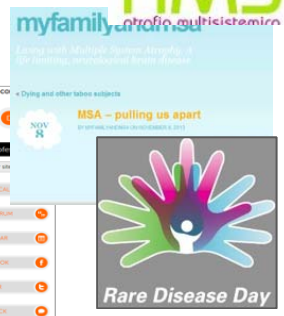
NORD®
National Organization for Rare Disorders



RARE CLINICAL DISEASES RESEARCH NETWORK



AMS



CURE MSA
KATHY SHIH MEMORIAL FOUNDATION

EUPATI
European Patients' Academy on Therapeutic Innovation

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Specialized Study Teams

- Require experienced team and quick learners
- Thorough indication training required by medical monitor
- Distribution of sites and countries require far global reach
- Understanding of KOL and specialist referral sites
- Team must be dynamic and highly engaged on recruitment, retention and quality
- Understanding patient pathway of treatment and close follow up with site for study inclusion

Site Engagement

- Rare diseases may be treated by key opinion leaders with limited GCP
- CRAs must be able to engage at deeper level of understanding
- Need increased attention to detail support sites through activation
- Increased remote interaction with site
- Sporadic on-site activity
- CRAs to follow up on patient retention with study staff
- Ability to flex approach as needed

Quality Planning and Discipline

Medical Input

- MM review eligibility
- Prompt safety reporting and closure of reported events
- Automate lab alerts as they relate to endpoints or values of interest

Data Quality

- CRA on site for first patient dosing day if possible
- Real time remote data review
- Timely listing review
- Set criterion for increased on site monitoring

Follow Through

- KPIs/KQIs relevant to site
- Identify trends across sites or data fields
- Retrain teams as needed
- Increase monitoring as required
- Proactively avoid patient replacement

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Final Thoughts

Engagement

Integration that transcends a transactional relationship

Creativity

“One eye on heaven, with both feet on the ground”

Commitment

“A sword in one hand, a pharmacopeia in the other”

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Questions?

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Thank You!

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