Design issues for pediatric trials (examples from rheumatology)

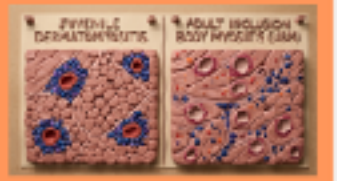
Brian Feldman MD, MSc, FRCPC
The Hospital for Sick Children, Toronto, Canada


Children are not just small adults. Proceed with caution.
EYE WASH

Design issues for pediatric trials

Trial architecture

Disease



Regulatory frameworks

Ranty

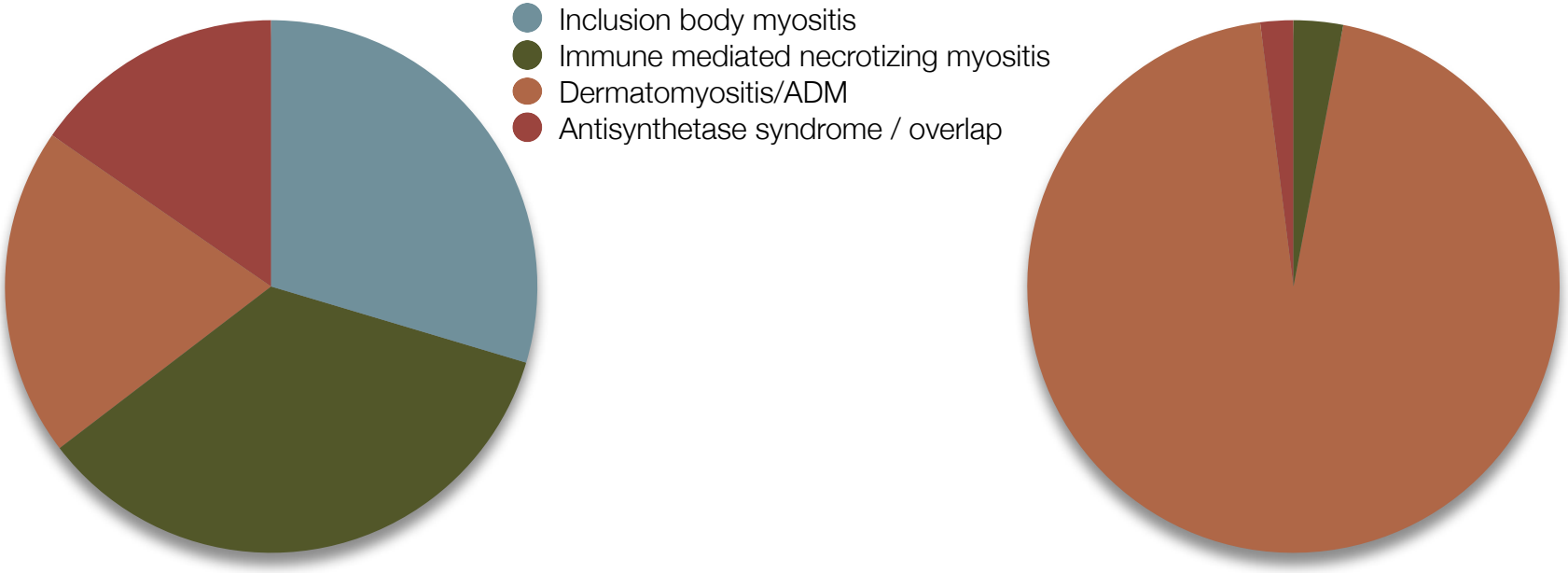
Ethics

Formulation

Outcome measures

Pharmacology

In children it's (almost) ALL dermatomyositis



Mariampillai K, Granger B, Amelin D, Guiguet M, Hachulla E, Maurier F, Meyer A, Tohmé A, Charuel J-L, Musset L, Allenbach Y, Benveniste O. Development of a New Classification System for Idiopathic Inflammatory Myopathies Based on Clinical Manifestations and Myositis-Specific Autoantibodies. JAMA Neurol. 2018;75:1528-1537.

Cancarini P, Nozawa T, Whitney K, Bell-Peter A, Marcuz JA, Taddio A, Guo J, Dover S, Feldman BM (2022). *Seminars in arthritis and rheumatism*, *57*

Epidemiology of Juvenile Dermatomyositis-What We Know and What More Is Needed? Int J Rheum Dis 2025;28(7):e70347.


CLINICAL TRIALS
NEED YOU!
HEALTH STUDY
WAITING AREA
JOIN US!
RECEPTION - PLEASE WAIT
Anyone...? Anyone here? Help us find new treatments? It's easy!


MEDICINE
TONIC
PERCY'S

Pharmaceutics **2011**, *3*, 53-72; doi: 10.3390/pharmaceutics3010053

OPEN ACCESS

pharmaceutics

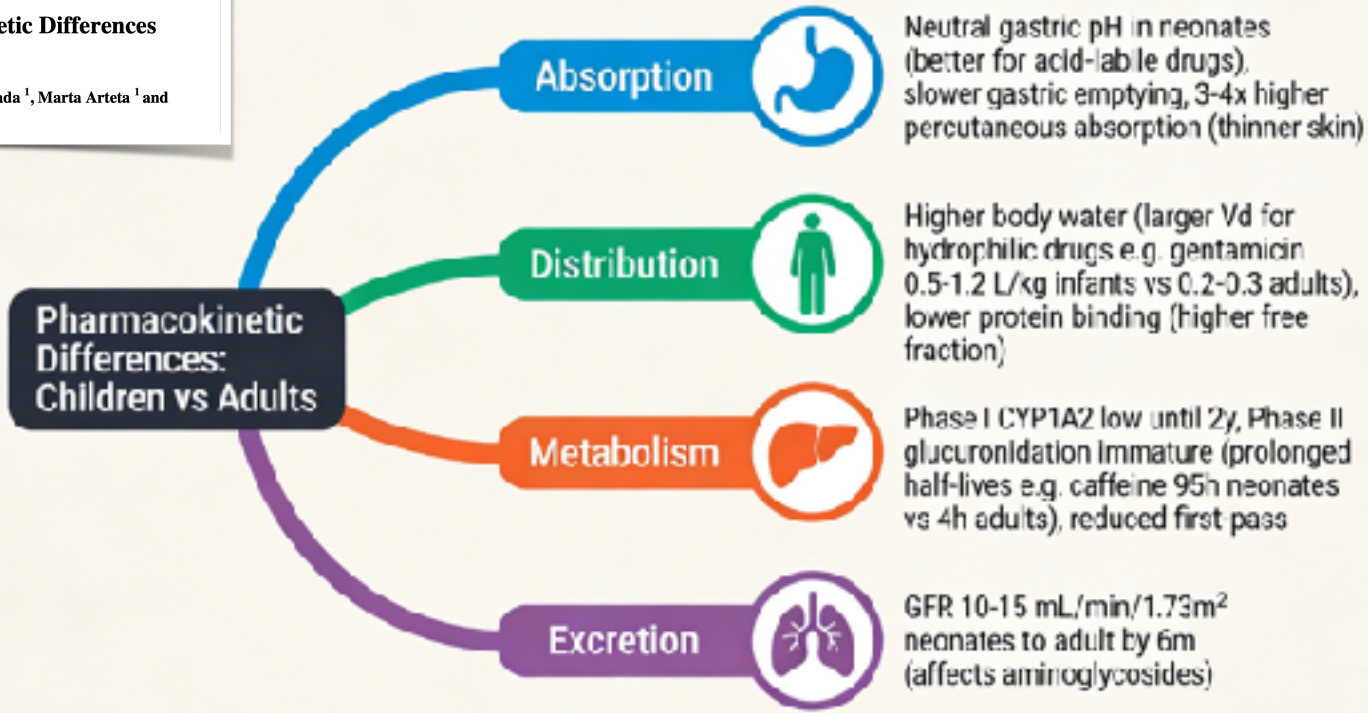
ISSN 1999-4923

www.mdpi.com/journal/pharmaceutics

Review

Factors and Mechanisms for Pharmacokinetic Differences between Pediatric Population and Adults

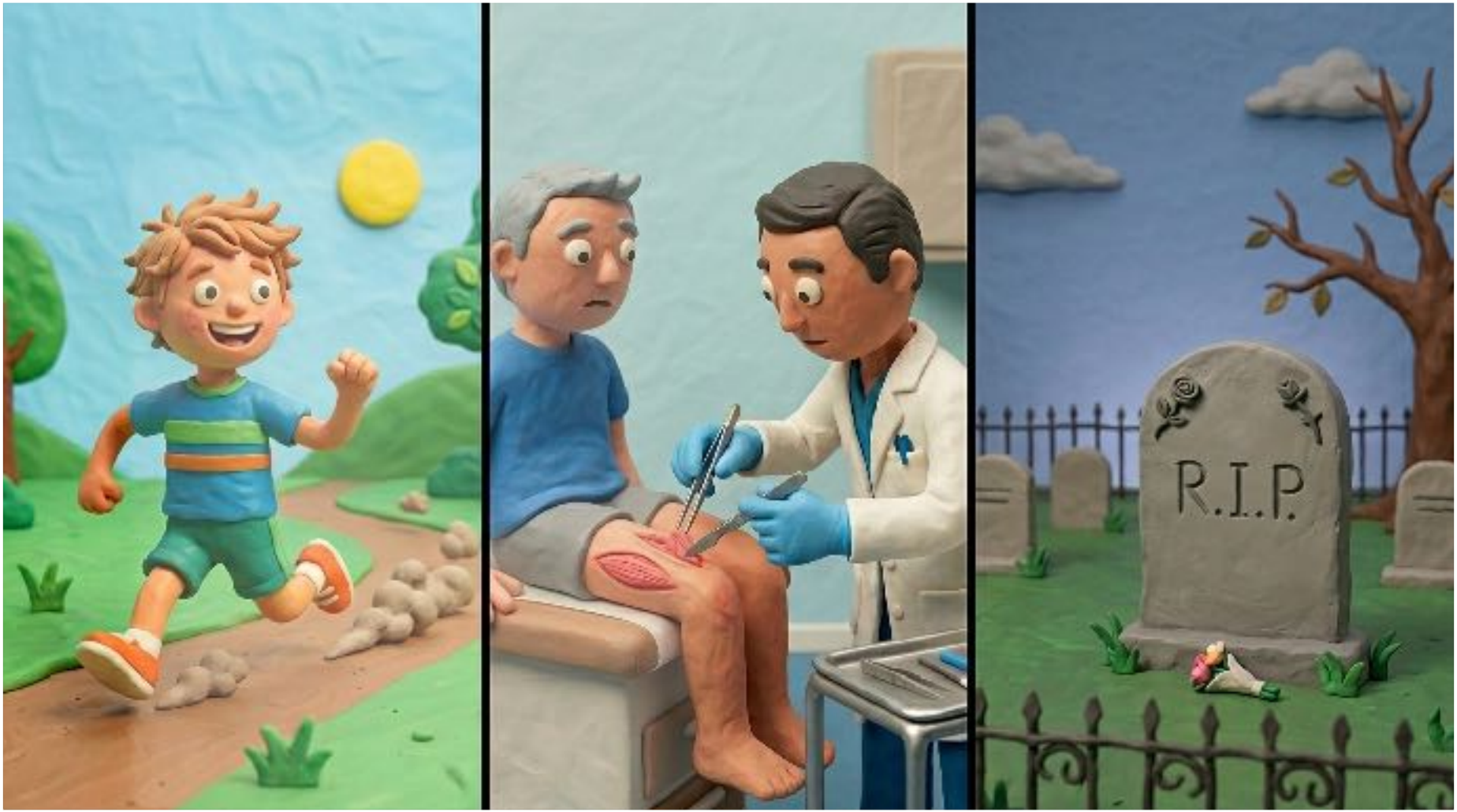
Eva Fernandez [1]*, Raul Perez [1], Alfredo Hernandez [1], Pilar Tejada [1], Marta Arteta [1] and Jose T. Ramos [2]*



Mycophenolate Mofetil (MMF)

Pharamacokinetics

PK feature	Children vs Adults
Apparent oral clearance (CL/F)	higher
PK variability in exposure at a given weight-based dose	higher
Need for dose individualization / TDM to hit exposure targets	higher
Required mg/kg dose to achieve comparable exposure	higher
Need for more frequent dosing	higher


R.I.P.

TLAR 1947

Arch Rheumatol 2020;35(1):97-106
doi: 10.5606/ArchRheumatol.2020.7548

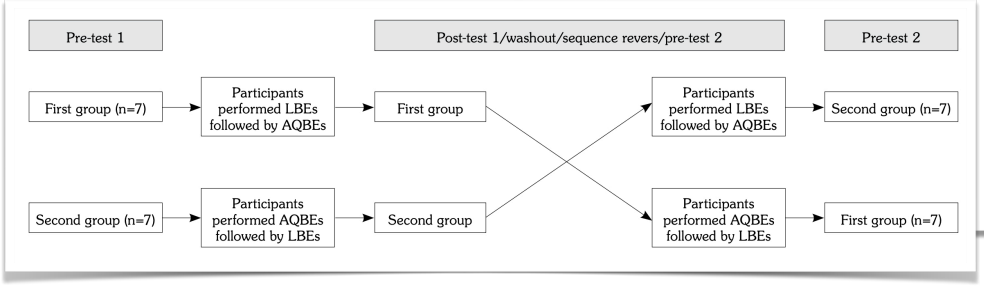
ORIGINAL ARTICLE

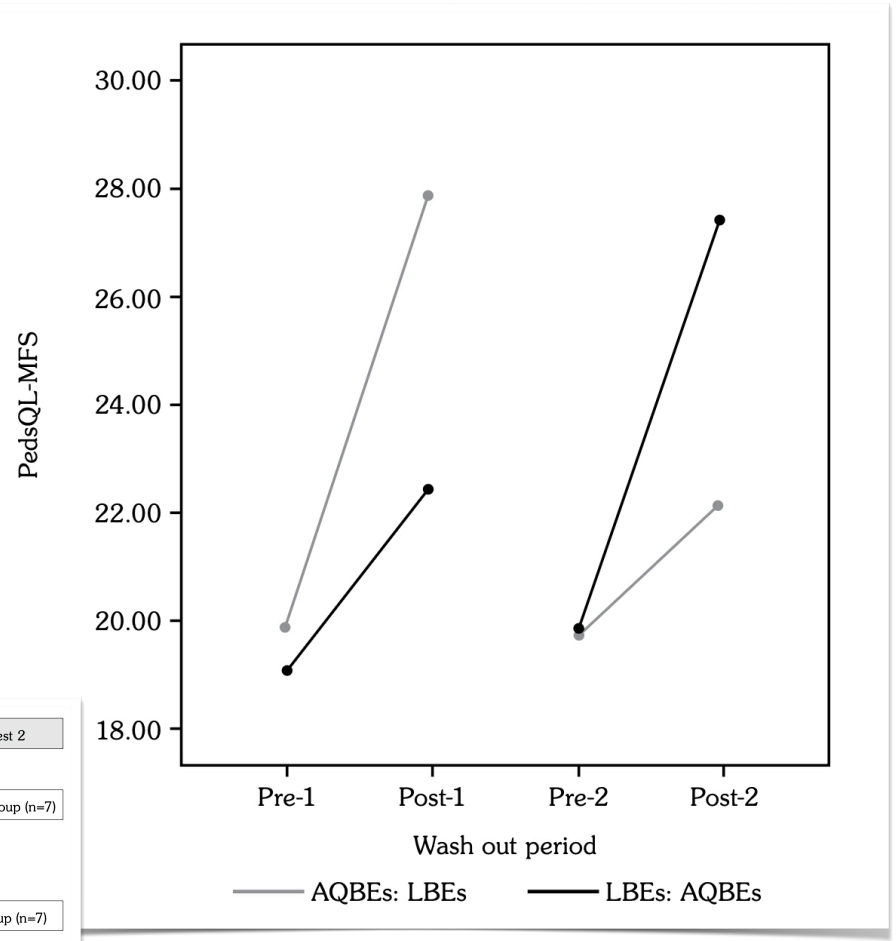
Assessment of the Clinical Effects of Aquatic-Based Exercises in the Treatment of Children With Juvenile Dermatomyositis: A 2×2 Controlled-Crossover Trial

Ahmed SAMHAN[1,4], Nermeen MOHAMED[1,4], Ragab ELNAGGAR[2,4], Waleed MAHMOUD[3,4]

[1]Department of Physical Therapy, New Kasr El-Aini Teaching Hospital, Faculty of Medicine, Cairo University, Cairo, Egypt
[2]Department of Physical Therapy for Pediatrics, Faculty of Physical Therapy, Cairo University, Cairo, Egypt
[3]Department of Basic Sciences, Faculty of Physical Therapy, Cairo University, Cairo, Egypt
[4]Department of Physical Therapy and Health Rehabilitation, College of Applied Medical Sciences, Prince Sattam Bin Abdulaziz University, Alkharj, Saudi Arabia

Fatigue



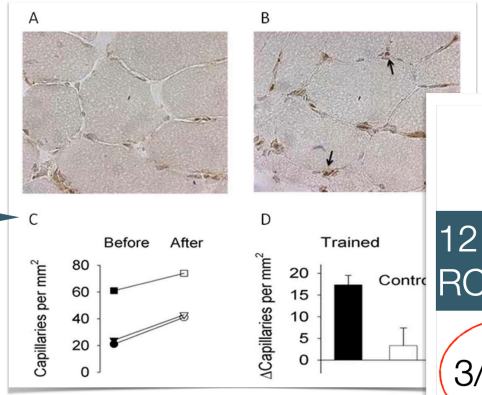


ARTHRITIS & RHEUMATOLOGY
Vol. 68, No. 7, July 2016, pp 1738–1750
DOI 10.1002/art.39624
© 2016, American College of Rheumatology

Endurance Exercise Improves Molecular Pathways of Aerobic Metabolism in Patients With Myositis

Li Alemo Munters,[1] Ingela Loell,[2] Elena Ossipova,[2] Joan Raouf,[2] Maryam Dastmalchi,[2] Eva Lindroos,[2] Yi-Wen Chen,[3] Mona Esbjörnsson,[2] Marina Korotkova,[2] Helene Alexanderson,[2] Kanneboyina Nagaraju,[3] Leslie J. Crofford,[4] Per-Johan Jakobsson,[2] and Ingrid E. Lundberg[2]

- 12 week endurance
- RCT
- N = 15
- Paired MM biopsies



12 wk cardio fitness RCT

3/group

MM bx, pre-post

microRNA

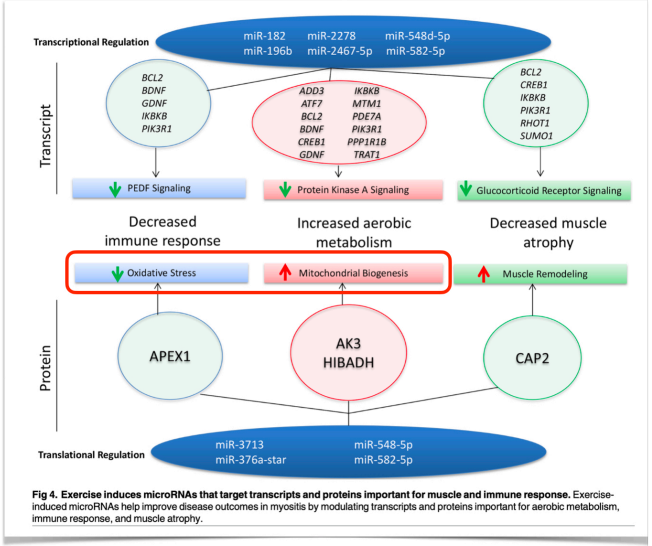


Fig 4. Exercise induces microRNAs that target transcripts and proteins important for muscle and immune response. Exercise-induced microRNAs help improve disease outcomes in myositis by modulating transcripts and proteins important for aerobic metabolism, immune response, and muscle atrophy.

Boehler JF, Hogarth MW, Barberio MD, Novak JS, Ghimbovschi S, Brown KJ, Alemo Munters L, Loell I, Chen Y-W, Gordish-Dressman H, Alexanderson H, Lundberg IE, Nagaraju K. Effect of endurance exercise on microRNAs in myositis skeletal muscle-A randomized controlled study. PloS one. 2017;12:e0183292.


UNCERTAINTY


PLACEBO

Clin Trials. 2018 April ; 15(2): 139–148. doi:10.1177/1740774517751118.

Barriers and facilitators to clinical trial participation among parents of children with pediatric neuromuscular disorders

Holly L Peay[1,2], **Barbara B Biesecker**[3], **Benjamin S Wilfond**[4], **Jill Jarecki**[5], **Kendall L Umstead**[3], **Diana M Escolar**[6], and **Aad Tibben**[7]

Perceived Barriers to Clinical Trial Participation

My child has not been enrolled in a clinical trial because…	**Combined**		**DBMD Only**		**SMA Only**	
	mean (*SD*)	***n***	**mean (*SD*)**	***n***	**mean (*SD*)**	***n***
My child could receive placebo (which is inactive medication).	4.52 (2.07)	195	4.66 (2.06)	102	4.38 (2.09)	93
I don't have enough information about the potential risks of clinical trials.	**4.21 (2.31)**	202	**3.61 (2.28)**	104	**4.86 (2.17)**	98
I don't have enough information about the day-to-day requirements of clinical trials.	**4.18 (2.31)**	202	**3.70 (2.21)**	104	**4.68 (2.31)**	98
The clinical trial may not be successful.	3.92 (1.95)	196	3.78 (1.98)	103	4.09 (1.92)	93
My child may not get any better in a clinical trial.	3.92 (1.96)	196	3.75 (2.02)	103	4.11 (1.89)	93
I don't have enough information about the potential benefits of clinical trials.	**3.80 (2.30)**	202	**3.27 (2.21)**	104	**4.37 (2.28)**	98
My child may not like being in a clinical trial.	3.71 (1.79)	195	3.72 (1.85)	103	3.70 (1.73)	92
My child could find the clinical trial too physically difficult.	3.53 (1.78)	196	3.47 (1.88)	103	3.59 (1.66)	93
For my child, there may be more risks than benefits.	3.51 (1.84)	196	3.23 (1.85)	103	3.82 (1.79)	93
My child could be hurt in a clinical trial.	3.50 (1.75)	196	3.24 (1.85)	103	3.78 (1.60)	93
I don't know about any clinical trials.	**3.34 (2.32)**	203	**2.86 (2.20)**	105	**3.86 (2.35)**	98
A clinical trial would put a strain on my family.	3.26 (1.80)	189	3.35 (1.81)	100	3.16 (1.78)	89
Being in a clinical trial would interrupt my child's daily routine.	3.26 (1.87)	189	3.18 (1.90)	100	3.35 (1.85)	89
The goals of clinical trials are not clear to me.	**3.12 (2.10)**	202	**2.64 (1.96)**	104	**3.62 (2.14)**	98
Being in a clinical trial would interrupt my daily routine.	2.93 (1.83)	189	2.81 (1.86)	100	3.06 (1.80)	89
Being in a clinical trial would take too much time.	2.86 (1.76)	189	2.72 (1.78)	100	3.01 (1.73)	89
I don't trust health care services or medical science in general.	1.97 (1.43)	195	1.84 (1.26)	102	2.12 (1.58)	93
I don't trust the medical teams involved in clinical trials.	1.93 (1.37)	189	1.81 (1.29)	100	2.06 (1.45)	89
I am not interested in the kinds of treatments provided in clinical trials.	1.82 (1.31)	203	1.79 (1.31)	105	1.85 (1.32)	98
It is wrong to conduct clinical trials on children.	1.80 (1.26)	203	1.64 (1.07)	105	1.97 (1.43)	98
Other parents of kids with my child's disease advised me not to put my child in a clinical trial.	1.33 (0.88)	189	1.23 (0.71)	100	1.45 (1.02)	89
People I trust advised me not to put my child in a clinical trial.	1.30 (0.79)	189	1.30 (0.82)	100	1.29 (0.76)	89

DBMD: Duchenne / Becker muscular dystrophy; SMA: spinal muscular atrophy; SD: standard deviation

Clin Trials. 2018 April ; 15(2): 139–148. doi:10.1177/1740774517751118.

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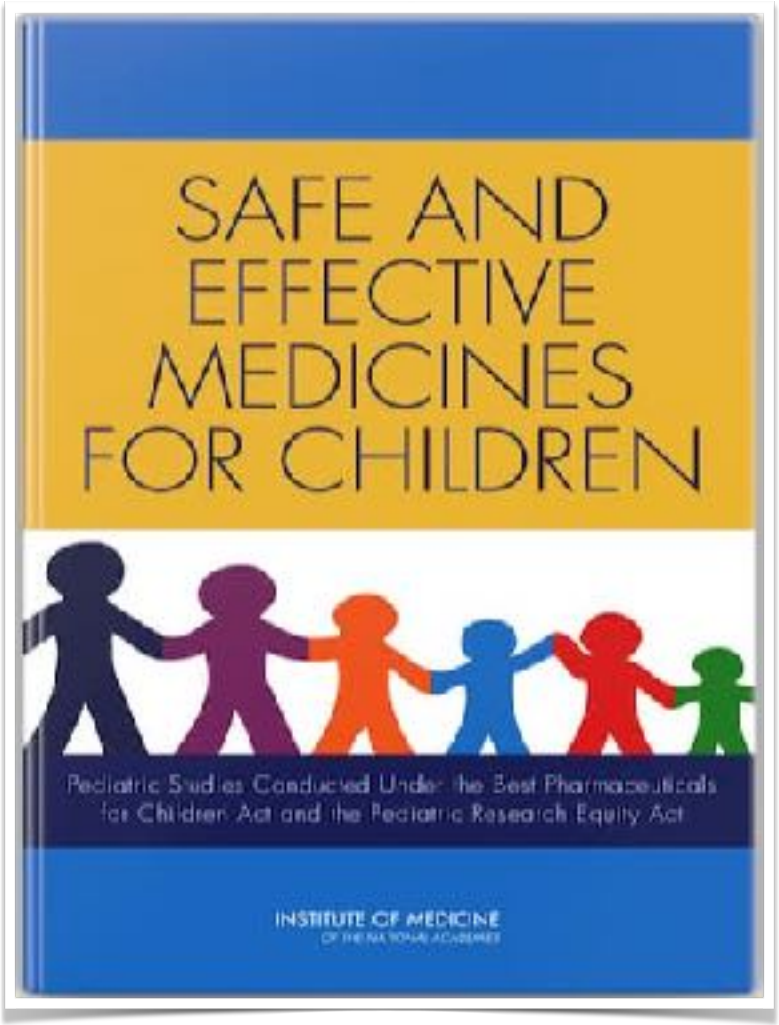
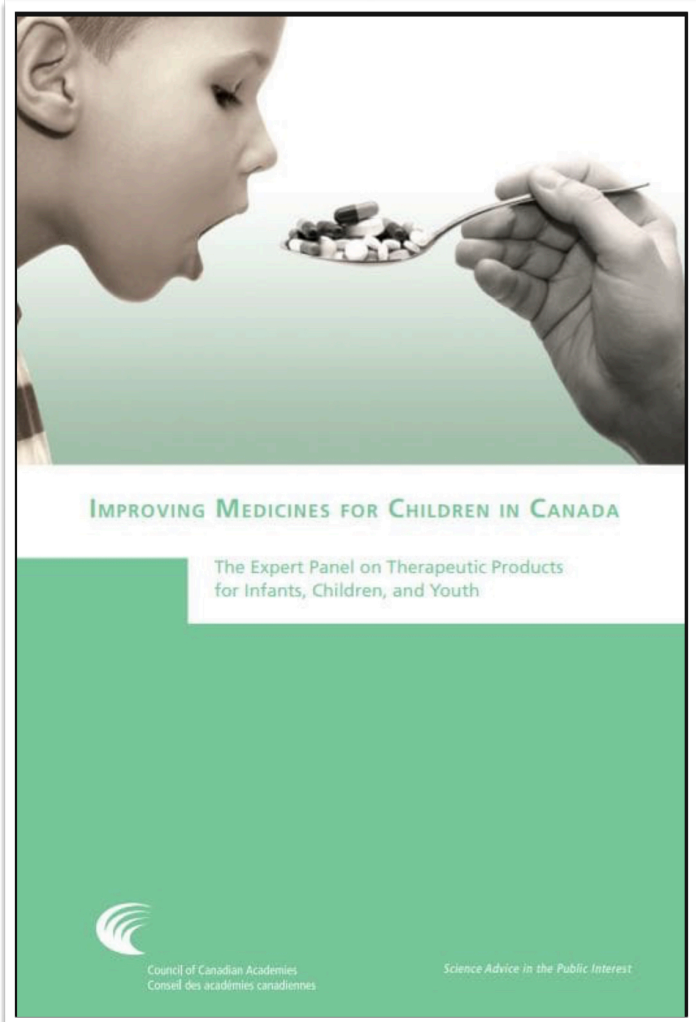
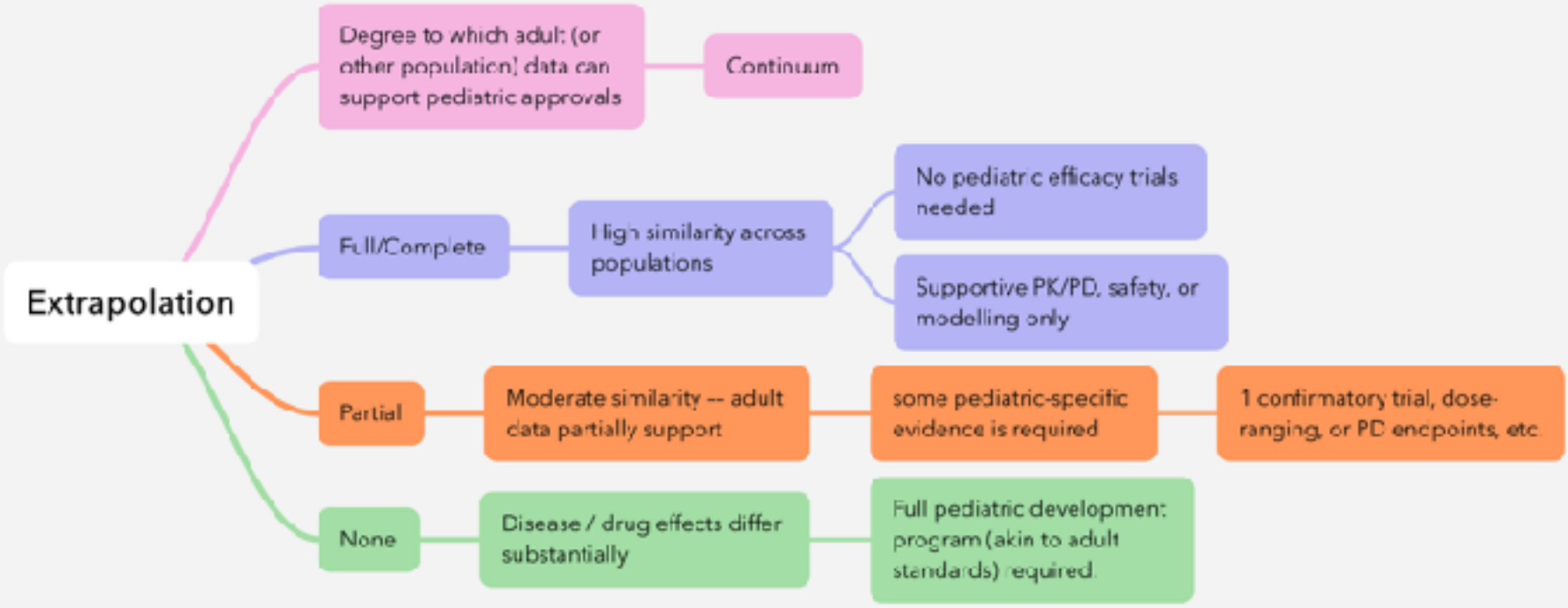

SAFE AND EFFECTIVE MEDICINES FOR CHILDREN
Pediatric Studies Conducted Under the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act
INSTITUTE OF MEDICINE


IMPROVING MEDICINES FOR CHILDREN IN CANADA
The Expert Panel on Therapeutic Products for Infants, Children, and Youth
Council of Canadian Academies
Conseil des académies canadiennes
Science Advice in the Public Interest

Region	Mandate Strength	Key Plan/Timing	Incentives	Key Features/Waivers
USA (PREA)	Strong (mandatory for new drugs)	Pediatric Study Plan (PSP); ~60–210 days pre-NDA	6-month exclusivity (BPCA)	Waivers/deferrals for impracticable/unsafe; **extrapolation** allowed
EU (EMA)	Strong (PIP required early)	Paediatric Investigation Plan (PIP); ~7 months review	6-month SPC extension; PUMA (10-year off-patent)	Biosimilars exempt; orphan incentives; unified EU scope
Health Canada	Weak (no mandate)	No formal PIP/PSP; voluntary	None specified	Relies on off-label; no enforcement power
Japan (PMDA)	Emerging (recent mandates)	Pediatric plans (post–2025 PMD Act); early encouraged	Reimbursement premiums	Japan-specific data; waivers common
China (NMPA)	Moderate (prioritizes)	Pediatric data encouraged; priority review	Faster approval (e.g., 377 days median)	Formulation focus; import-heavy

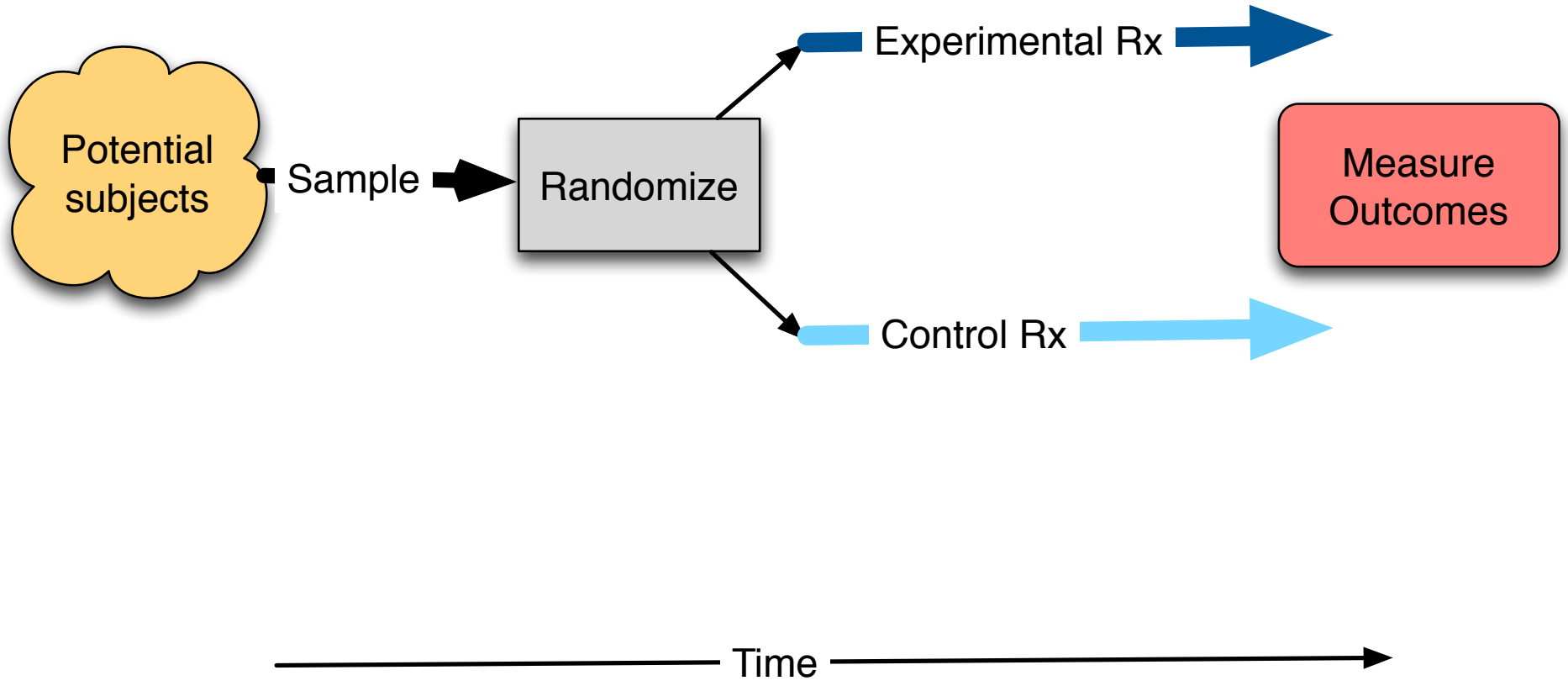

Extrapolation
Degree to which adult (or other population) data can support pediatric approvals
Continuum
Full/Complete
High similarity across populations
No pediatric efficacy trials needed
Supportive PK/PD, safety, or modelling only
Partial
Moderate similarity -- adult data partially support
some pediatric-specific evidence is required
1 confirmatory trial, dose-ranging, or PD endpoints, etc
None
Disease / drug effects differ substantially
Full pediatric development program (akin to adult standards) required

Considerations for trial design

Need
Evidence

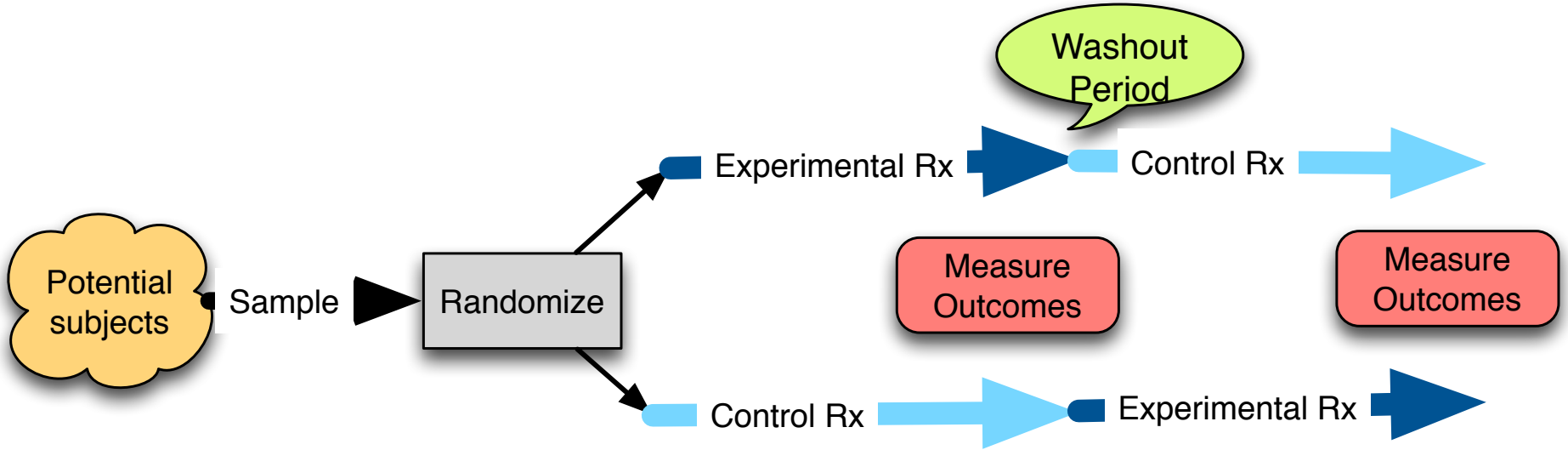
Difficult
Accrual

Less
Rigour



Parallel groups, RCT

Increase accrual → make trials more acceptable → limit placebo



Crossover trial

Time

Paediatric rheumatology

RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Lengthening sleep reduces pain in childhood arthritis: a crossover randomised controlled trial

Hayyah Clairman ,[1] Saunya Dover,[1] George Tomlinson,[2] Dean Beebe,[3,4] Bonnie Cameron,[5] Ronald M Laxer,[5] Deborah Levy,[5] Indra Narang,[6] Susan Paetkau,[5] Rayfel Schneider,[5] Lynn Spiegel,[5] Samantha Stephens,[7] Jennifer Stinson,[1] Shirley Tse,[5] Shelly Weiss,[8] Kristi Whitney,[9] Brian M Feldman[1,5]

Cross-over

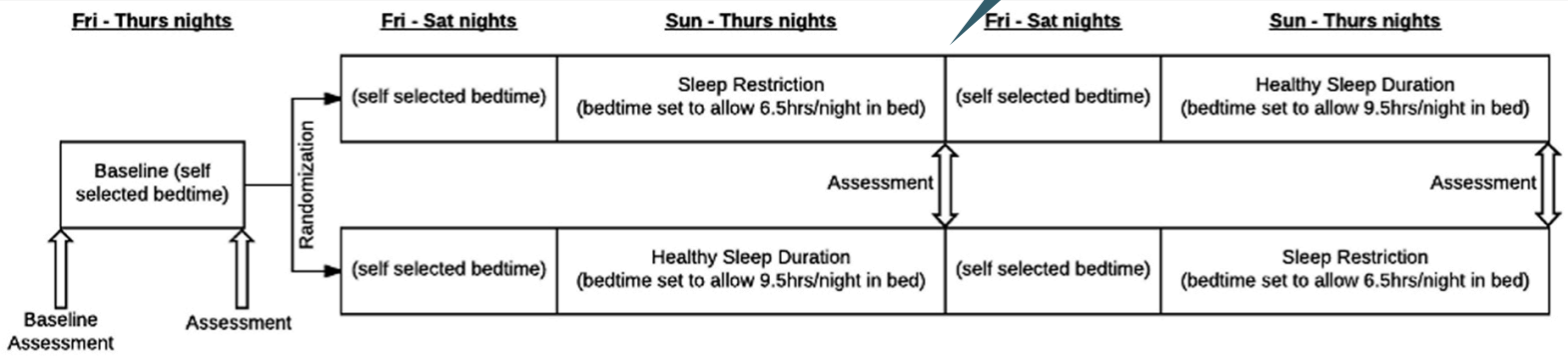
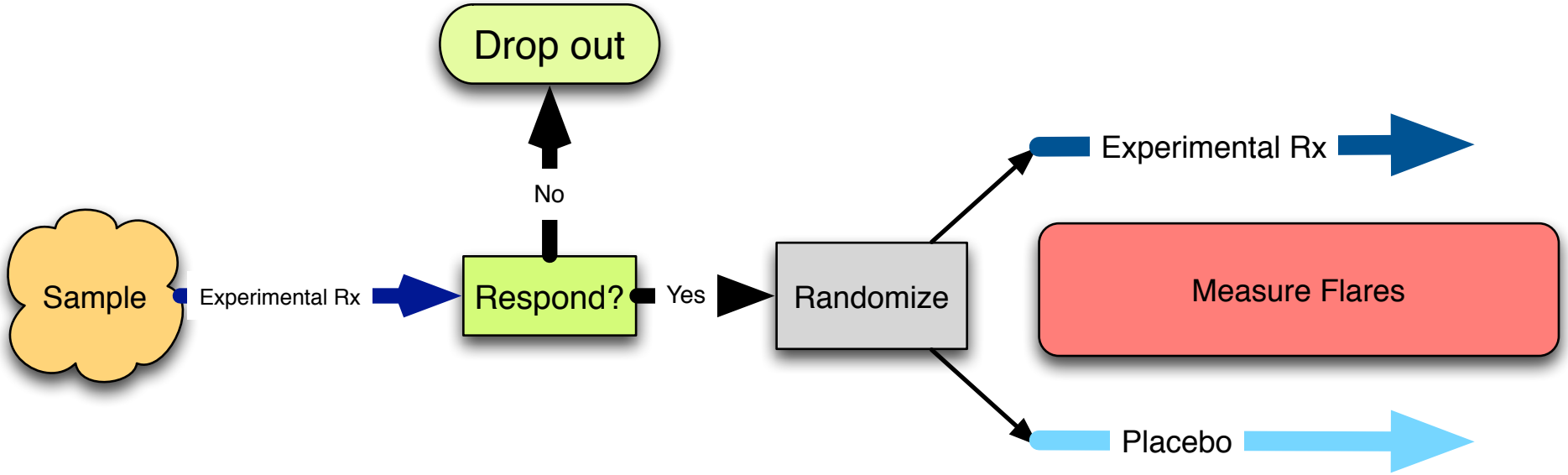
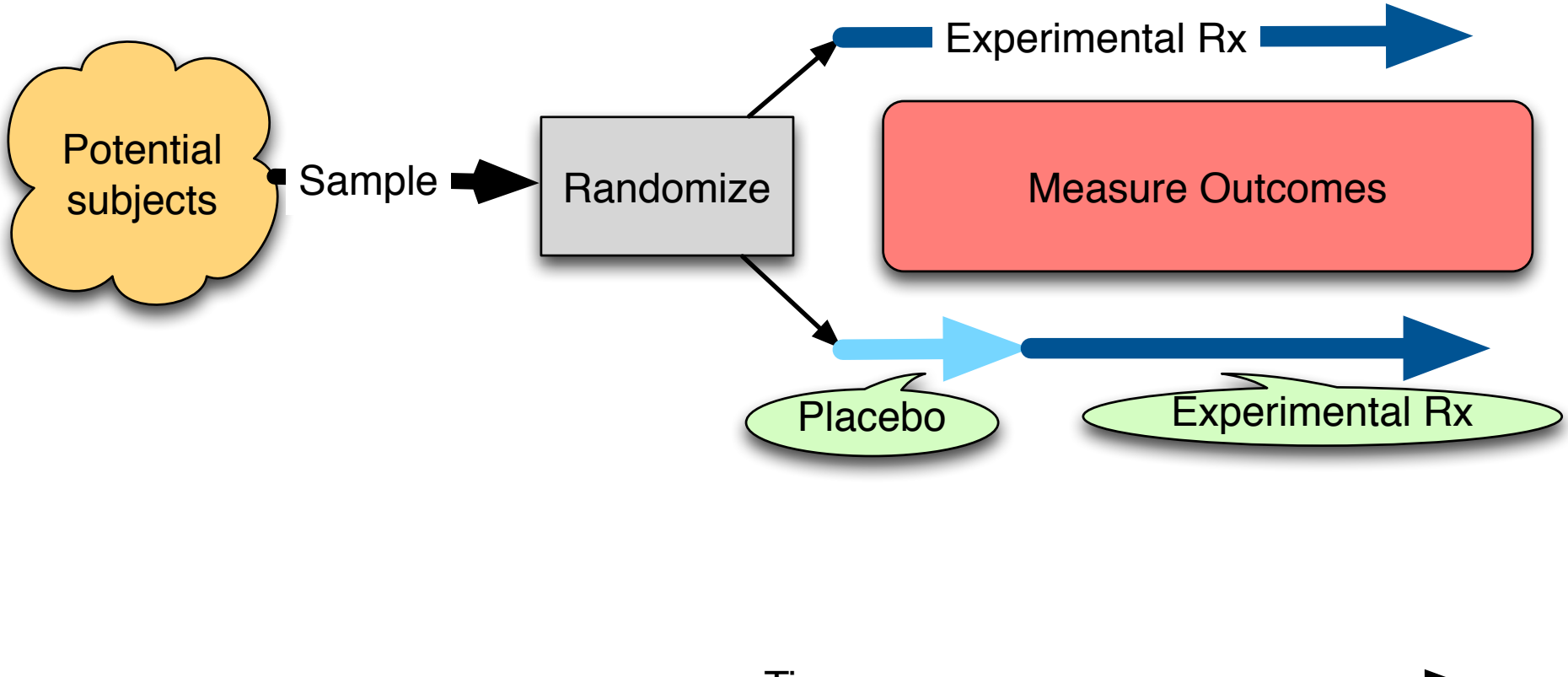


Figure 1 Study protocol and duration of follow-up.



Withdrawal Trial

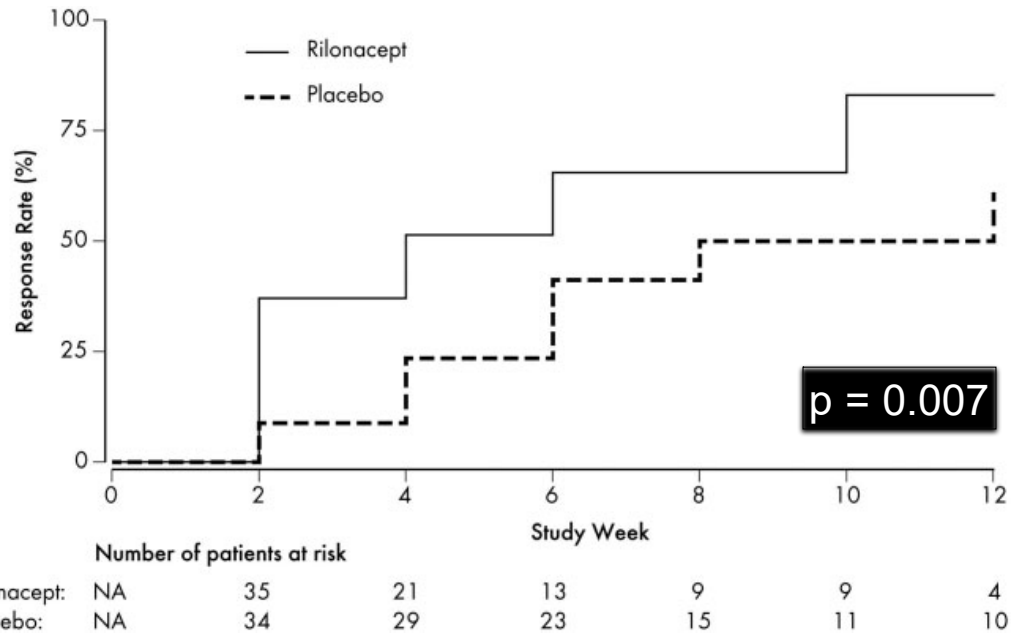
Time



Randomized placebo phase

ARTHRITIS & RHEUMATOLOGY
Vol. 66, No. 9, September 2014, pp 2570–2579
DOI 10.1002/art.38699

Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy and Safety of Rilonacept in the Treatment of Systemic Juvenile Idiopathic Arthritis



Avoiding frequentist

hypothesis testing

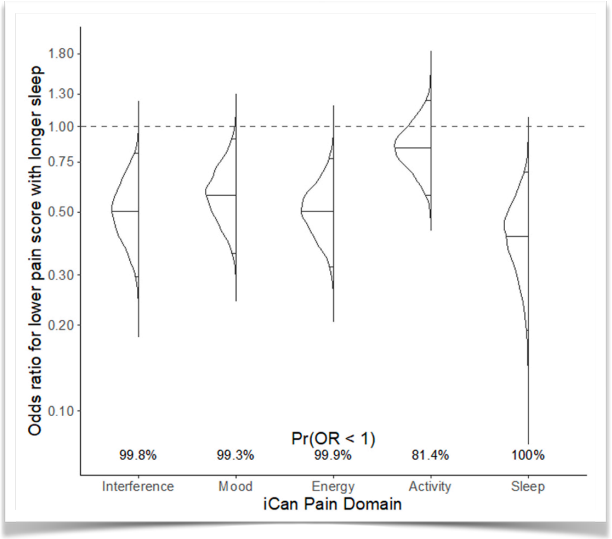
Paediatric rheumatology

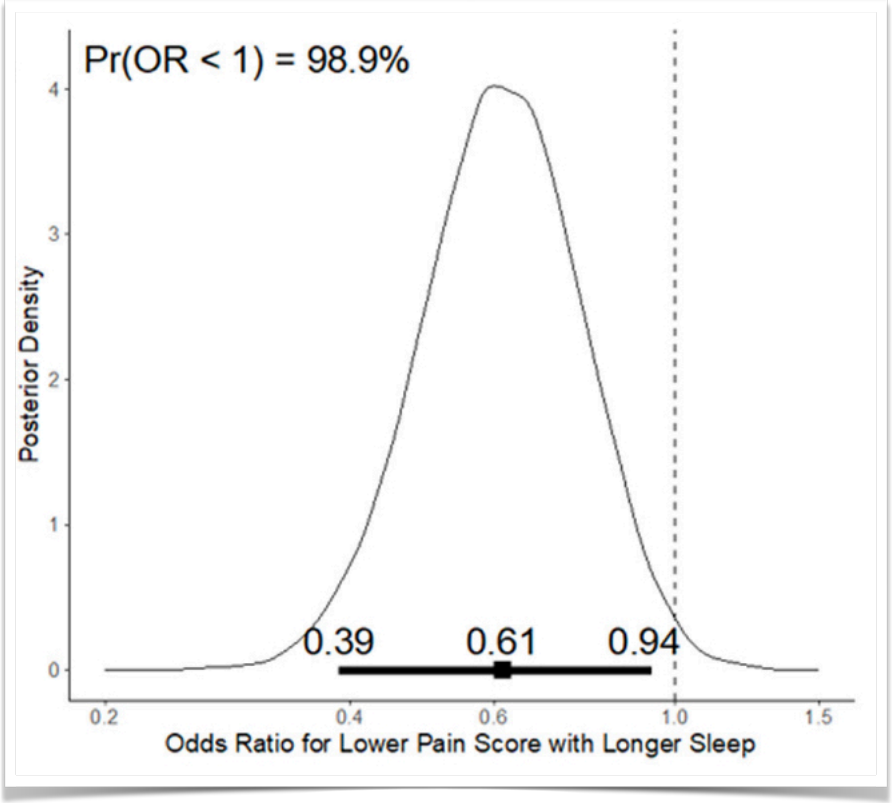
RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Lengthening sleep reduces pain in childhood arthritis: a crossover randomised controlled trial

Hayyah Clairman ,[1] Saunya Dover,[1] George Tomlinson,[2] Dean Beebe,[3,4] Bonnie Cameron,[5] Ronald M Laxer,[5] Deborah Levy,[5] Indra Narang,[6] Susan Paetkau,[5] Rayfel Schneider,[5] Lynn Spiegel,[5] Samantha Stephens,[7] Jennifer Stinson,[1] Shirley Tse,[5] Shelly Weiss,[8] Kristi Whitney,[9] Brian M Feldman[1,5]





The Journal of Rheumatology 2021;48:434–41
doi:10.3899/jrheum.191375
First Release January 15 2021

The Journal of Rheumatology

The Effect of Creatine Supplementation on Muscle Function in Childhood Myositis: A Randomized, Double-blind, Placebo-controlled Feasibility Study

Saunya Dover[1], Samantha Stephens[2], Jane E. Schneiderman[3], Eleanor Pullenayegum[4], Greg D. Wells[5], Deborah M. Levy[6], Jo-Anne Marcuz[7], Kristi Whitney[7], Andreas Schulze[8], Ingrid Tein[9], and Brian M. Feldman[10]

Ben-Eltriki *et al.*
BMC Medical Research Methodology (2024) 24:229
https://doi.org/10.1186/s12874-024-02272-9

BMC Medical Research Methodology

RESEARCH Open Access

Adaptive designs in clinical trials: a systematic review-part I

Mohamed Ben-Eltriki[1,2,3*], Aisha Rafiq[1], Arun Paul[1], Devashree Prabhu[2], Michael O. S. Afolabi[4], Robert Baslhaw[2,5], Christine J Neilson[6], Michelle Driedger[5], Salaheddin M Mahmud[5], Thierry Lacaze-Masmonteil[7], Susan Marlin[8], Martin Offringa[10,11], Nancy Butcher[11,12], Anna Heath[11,13,14] and Lauren E Kelly[1,2,9,15*]

The Journal of Rheumatology

The Journal of Rheumatology

Pilot study of the juvenile dermatomyositis consensus treatment plans: a CARRA Registry study

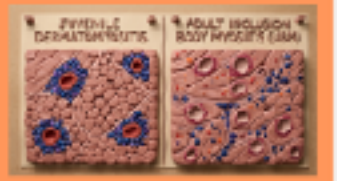
Kuan Liu, George Tomlinson, Ann M. Reed, Adam M. Huber, Olli Saarela, Sharon M. Bout-Tabaku, Megan Curran, Jeffrey A. Dvergsten, Barbara A. Eberhard, Lawrence K. Jung, Susan Kim, Sarah Ringold, Kelly A. Rouster-Steven, Melissa Tesher, Dawn M. Wahezi and Brian M. Feldman, for the CARRA Registry Investigators

DOI: 10.3899/jrheum.190494
http://www.jrheum.org/content/early/2020/03/25/jrheum.190494

Design issues for pediatric trials

Trial architecture

Disease



Regulatory frameworks

Ranty

Ethics

Formulation

Outcome measures

Pharmacology