BIRTH ASPHYXIA ASSESSMENT & LANDSCAPING

Grayson S, Hergott D, Secor A, Lingappa J

June 7, 2019

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STRATEGIC ANALYSIS, RESEARCH & TRAINING CENTER

Department of Global Health | University of Washington

BIRTH ASPHYXIA START TEAM

Shira Grayson

Project Manager

Dianna Hergott

Research Assistant

Andrew Secor

Research Assistant

Jairam Lingappa

Faculty Lead

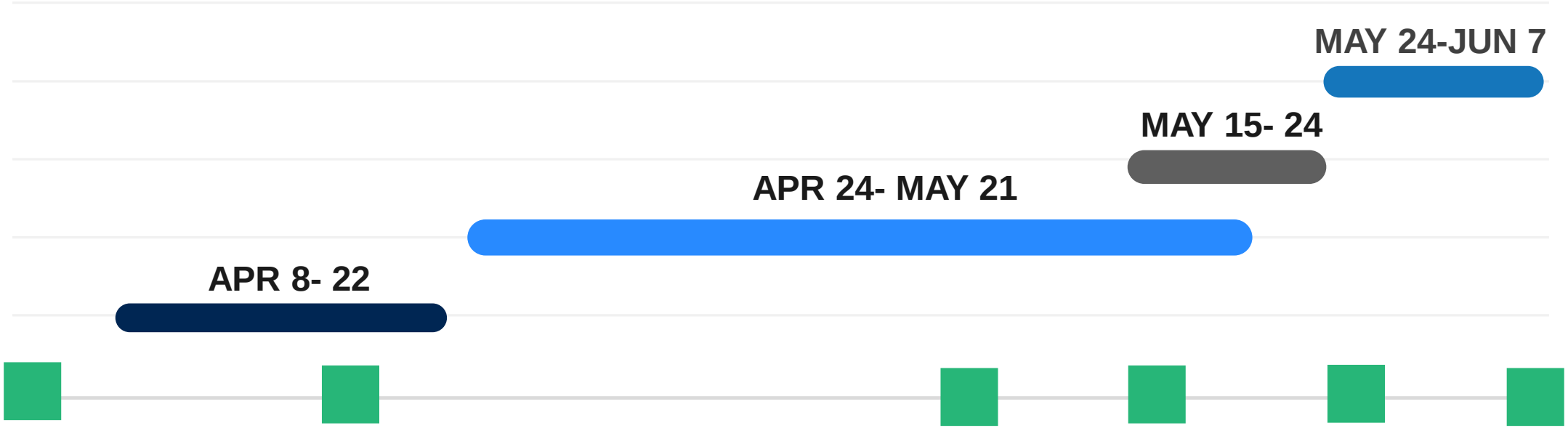
PROJECT OVERVIEW

Review BMGF Sources & Develop Research Strategy

Effect Size Research (Aim 1)

Candidate Drug Trial Research (Aim 2)

Refine Deliverables



Scoping Meeting
APR 3

1st SME Call
APR 15

2nd SME Call
MAY 13

Check-in Meeting
MAY 15

Submit Deliverable
MAY 31

Final Meeting
JUN 7

WORK ORDER OBJECTIVES

Intervention Effect Size (Aim 1)

- Labor & delivery
- Neonatal resuscitation
- Therapeutic hypothermia
- Drug-based interventions

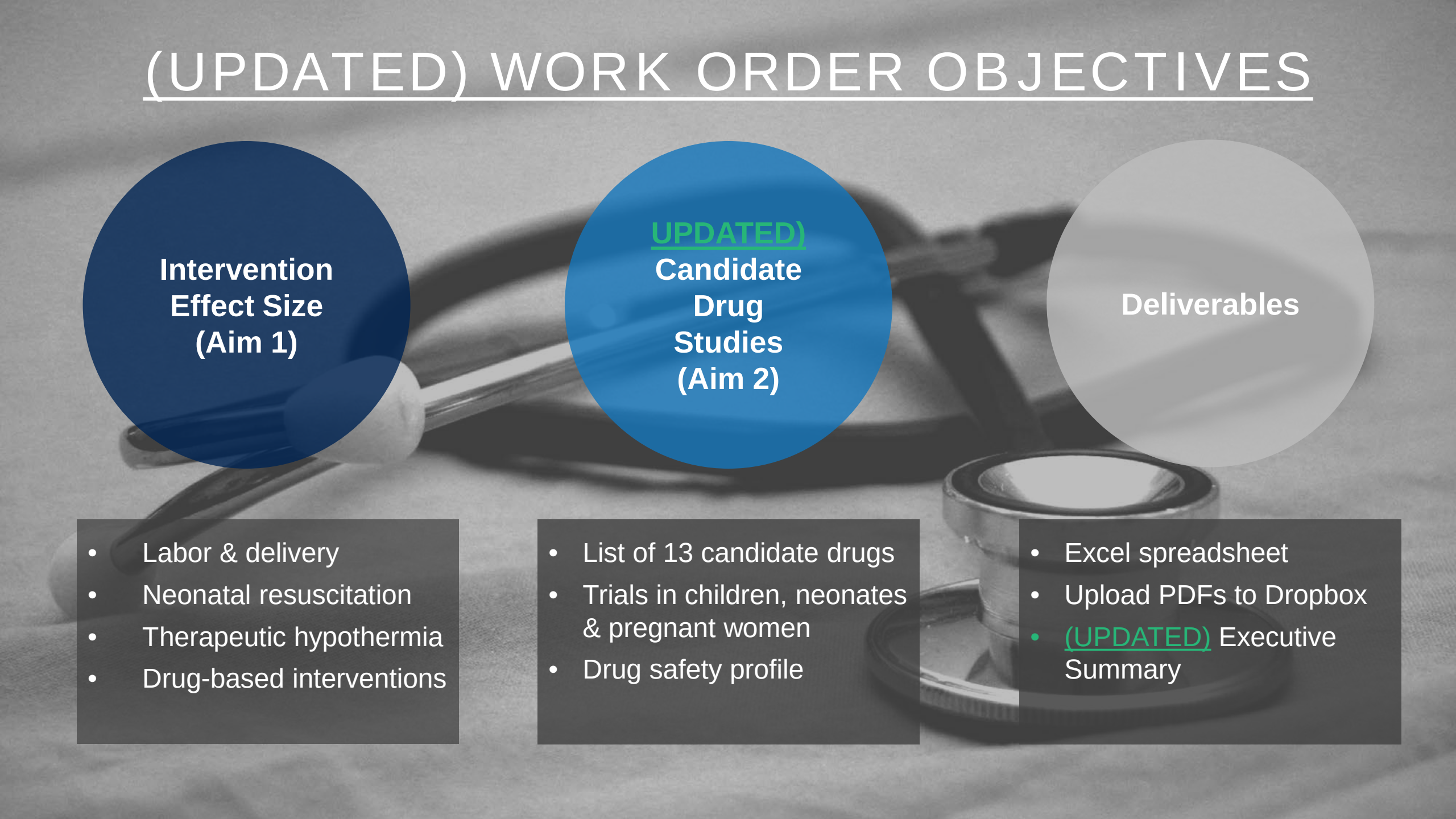
HIE Burden Estimates (Aim 2)

- Incidence of mild, moderate and severe HIE
- Facility level-specific
- Geography-specific (HIC/LMIC)

Deliverables

- Excel spreadsheet
- Upload PDFs to Dropbox

(UPDATED) WORK ORDER OBJECTIVES



Intervention Effect Size (Aim 1)

- Labor & delivery
- Neonatal resuscitation
- Therapeutic hypothermia
- Drug-based interventions

(UPDATED) Candidate Drug Studies (Aim 2)

- List of 13 candidate drugs
- Trials in children, neonates & pregnant women
- Drug safety profile

Deliverables

- Excel spreadsheet
- Upload PDFs to Dropbox
- (UPDATED) Executive Summary

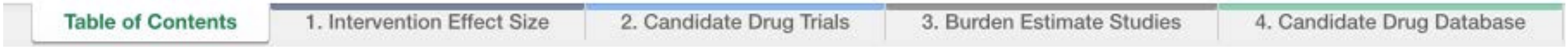
WORKBOOK DELIVERABLE FORMAT

1. Intervention Effect Size: Outcomes from studies of clinical interventions given to encephalopathic term infants with evidence of perinatal hypoxic insult

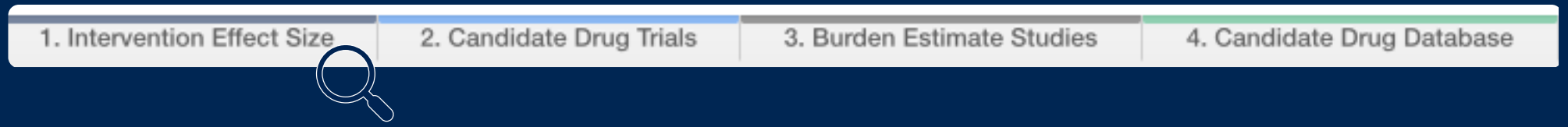
2. Candidate Drug Trials: Studies of BMGF-identified 13 priority drugs given to pregnant women and young children with reported adverse events, toxicology, or pharmacokinetic/pharmacodynamic information

3. Burden Estimate Studies: Estimates of intrapartum-related neonatal health burden with a focus on hypoxic ischemic encephalopathy (HIE)

4. **Candidate Drug Database:** Line listing of all clinical trials in target populations registered in the NIH clinical trails (clinicaltrials.gov) of BMGF-identified list of 13 priority drugs



EFFECT SIZE STUDIES (AIM 1)



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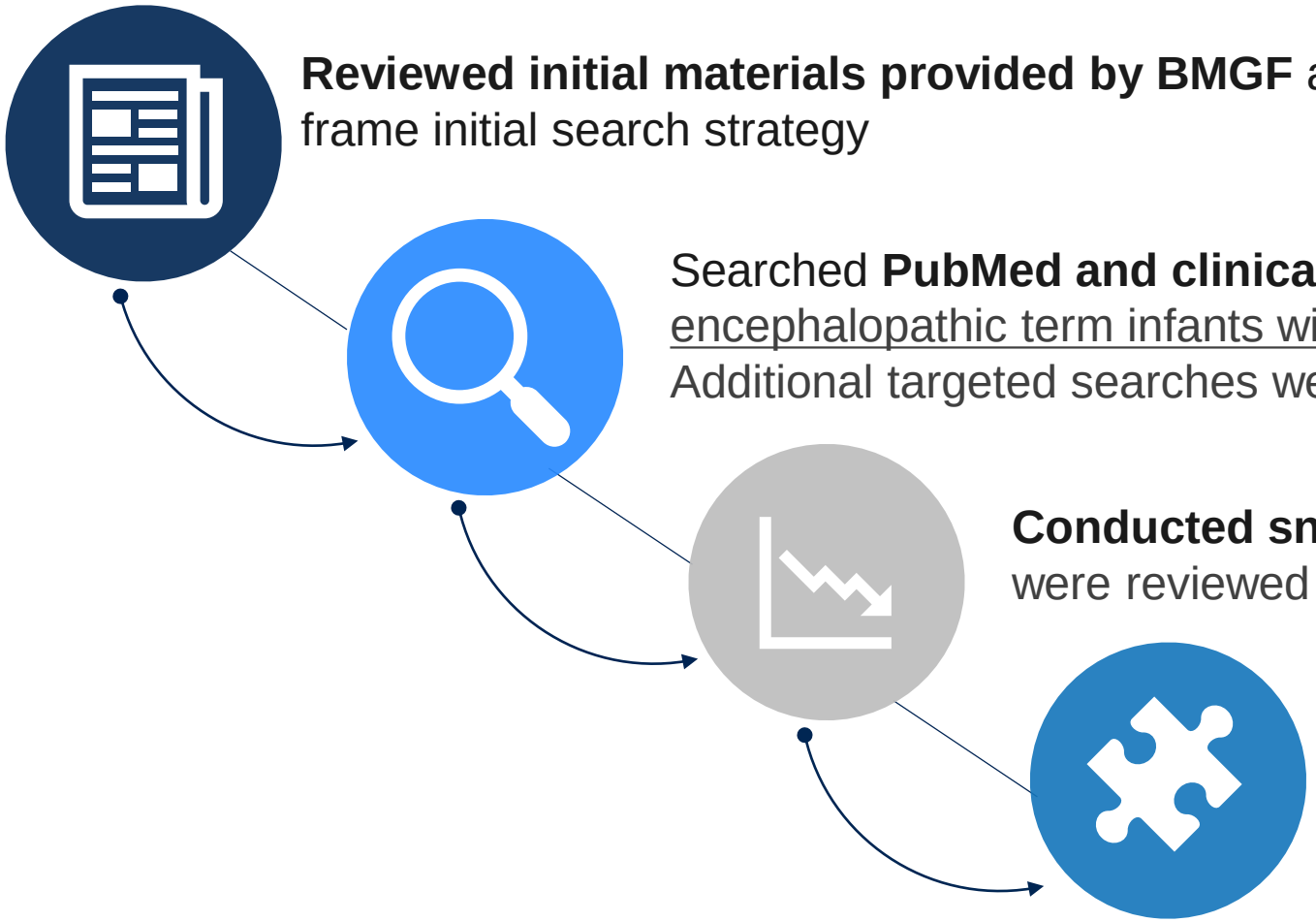
STRATEGY TO IDENTIFY EFFECT SIZE STUDIES

AIM 1 METHODOLOGY



Reviewed initial materials provided by BMGF and used most relevant sources to frame initial search strategy

Searched **PubMed and clinicaltrials.gov** for clinical interventions given to encephalopathic term infants with evidence of perinatal hypoxic insult. Additional targeted searches were conducted for the 13 high priority drugs

Conducted snowball sampling, where highly relevant articles were reviewed for relevant references

Extracted data from relevant papers and compiled high-priority review papers

→ 1. Intervention Effect Size

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TARGETED SEARCH CRITERIA

CLINICAL INTERVENTIONS TARGETED

- Therapeutic hypothermia
- Drug-based interventions
- Neonatal resuscitation
- Labor and delivery

TERMS USED TO IDENTIFY PERINATAL HYPOXIC INSULT

- Asphyxia neonatorum
- Birth asphyxia
- Neonatal encephalopathy
- Hypoxic ischemic encephalopathy
- Intrapartum mortality

PUBLISHED ON OR AFTER THE YEAR 2000

- Some earlier results included as part of meta-analyses

SELECTION PROCESS FOR EFFECT SIZE STUDIES

40 BMGF Resources +
525 Searched Studies
Reviewed

520 excluded for lack of relevance or repeated data

45 Studies Included in Final Deliverable
- 7 from BMGF
- 38 from searched papers

34 Effect Size Studies
- 16 Therapeutic hypothermia
- 10 Drug-based
- 5 Resuscitation
- 2 Other
- 1 Multiple

11 High-relevance Reviews

SELECTION PROCESS FOR EFFECT SIZE STUDIES

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520 excluded for lack of relevance or repeated data

45 Studies Included in Final Deliverable
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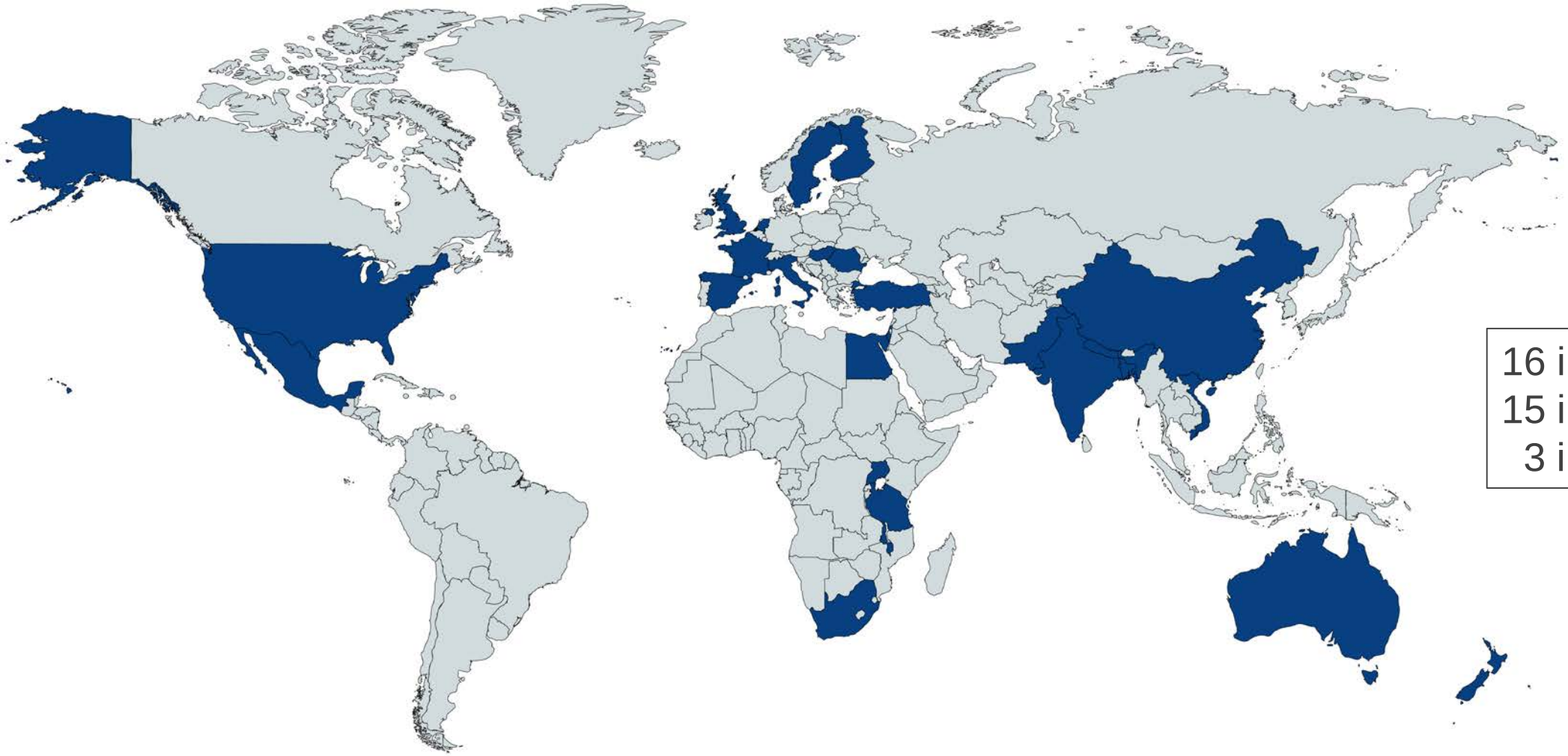
- 38 from searched papers

34 Effect Size Studies
- 16 Therapeutic hypothermia
- **10 Drug-based**
- 5 Resuscitation
- 2 Other
- 1 Multiple

11 High-relevance Reviews

Drugs included:
Erythropoietin
Magnesium sulfate
Xenon (with hypothermia)
Barbiturates
Melatonin
Allopurinol
Topiramate
Ascorbic acid
Ibuprofen
Phenobarbital

GEOGRAPHIC SPREAD OF EFFECT SIZE STUDIES



16 in LMICs
15 in HICs
3 in Both

EFFECT SIZE STUDY COMPOSITION

Facility Type	# Studies (% Total)
Tertiary Care	30 (88%)
Community-based	1 (3%)
Multiple	3 (9%)
HIE Severity	**# Studies (% Total)**
Moderate/Severe	13 (38%)
Low/Moderate	11 (33%)
Unknown	10 (29%)
Study Type	**# Studies (% Total)**
RCT	23 (68%)
Meta-analysis	6 (18%)
Retrospective	3 (9%)
Non-RCT Prospective	2 (6%)

PRIORITIZED EFFECT SIZE STUDIES

Intervention	Study	Sample Size	Effect Measure	Outcome	Effect Size
Therapeutic hypothermia	Jacobs, 2013	N=1,501	Relative risk (treatment vs. no treatment)	1. Death or major neurodevelopmental disability (NDD) 2. Mortality 3. Major NDD	**1. 0.75 (0.68 - 0.83)** **2. 0.75 (0.64 - 0.88)** **3. 0.67 (0.55 - 0.80)**
Erythropoietin	Razak, 2019	N=424	Relative risk (treatment vs. placebo or no treatment)	1. Death 2. Cerebral palsy 3. Moderate to severe cognitive impairment	1. 0.89 (0.49 - 1.32) **2. 0.47 (0.27 - 0.80)** **3. 0.49 (0.28 - 0.85)**
Allopurinol	Chaudhari, 2012	N=114	Relative risk (treatment vs. placebo or no treatment)	1. Death or severe NDD 2. Mortality (during infancy) 3. Severe quadriplegia in surviving infants	1. 0.78 (0.56 - 1.08) 2. 0.88 (0.56 - 1.38) 3. 0.59 (0.28 - 1.27)
Resuscitation training	Deorari, 2001	N=25,713	% of births (pre- vs. post-intervention)	1. All-cause neonatal mortality 2. Hypoxia-related neonatal mortality 3. Seizures due to hypoxia	1. 3.7% vs. 3.5% 2. 1.6% vs. 1.1% 3. 0.3% vs. 0.5%

HIGHLIGHTS

1. Therapeutic hypothermia has been studied in both high- and low-resource settings and has shown reductions in mortality and morbidity (Jacobs 2013)

2. Meta-analysis of erythropoietin showed reduction in risk of brain injury, cerebral palsy and cognitive impairment but not mortality (Razak 2019)

3. Meta-analyses of allopurinol and barbiturates did not have enough high-quality data to determine effect (Chaudhari 2012, Young 2016)

4. Other drugs and interventions (e.g. resuscitation training) have shown mixed results and/or require stronger evidence bases (e.g. few studies and/or small sample sizes)

5. No identified effect size studies in 13 high-priority drugs

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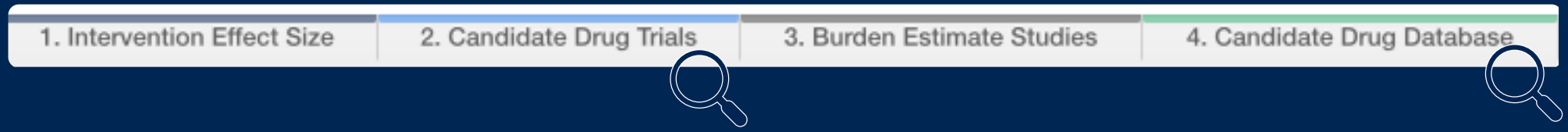
CANDIDATE DRUG TRIALS (AIM 2)



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CRITERIA USED TO IDENTIFY MOST RELEVANT STUDIES IN CANDIDATE DRUGS

1. **Limited to Clinical Trials** – *most likely to have information on adverse events*

2. **Restricted Age** – *used various filters to find studies in which children were given the drug*

3. **Studies in Pregnant Women** – *used text strings and searched inclusion/exclusion criteria*

4. **No restriction on condition** – *looked for studies that used drug for any condition, not restricted to HIE*

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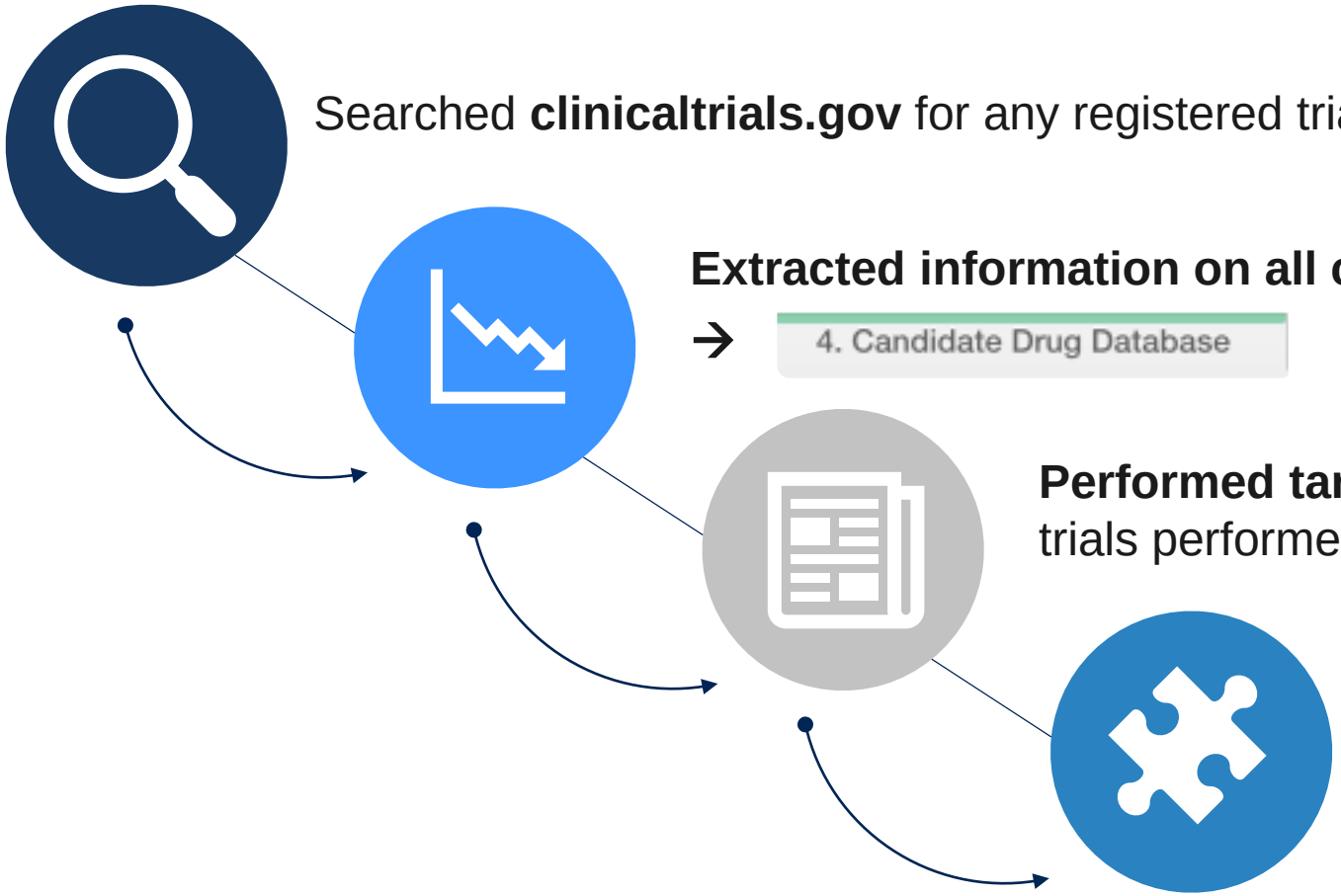
STRATEGY TO IDENTIFY CLINICAL TRIALS ON CANDIDATE DRUGS

AIM 2 METHODOLOGY



Searched **clinicaltrials.gov** for any registered trials in target populations

Extracted information on all clinical trials in target populations

→ 4. Candidate Drug Database

Performed targeted search in PubMed, restricted to clinical trials performed in neonates, children, and/or pregnant women

Extracted data from most relevant trials

→ 2. Candidate Drug Trials

SCREENSHOT OF TRIAL DATABASE

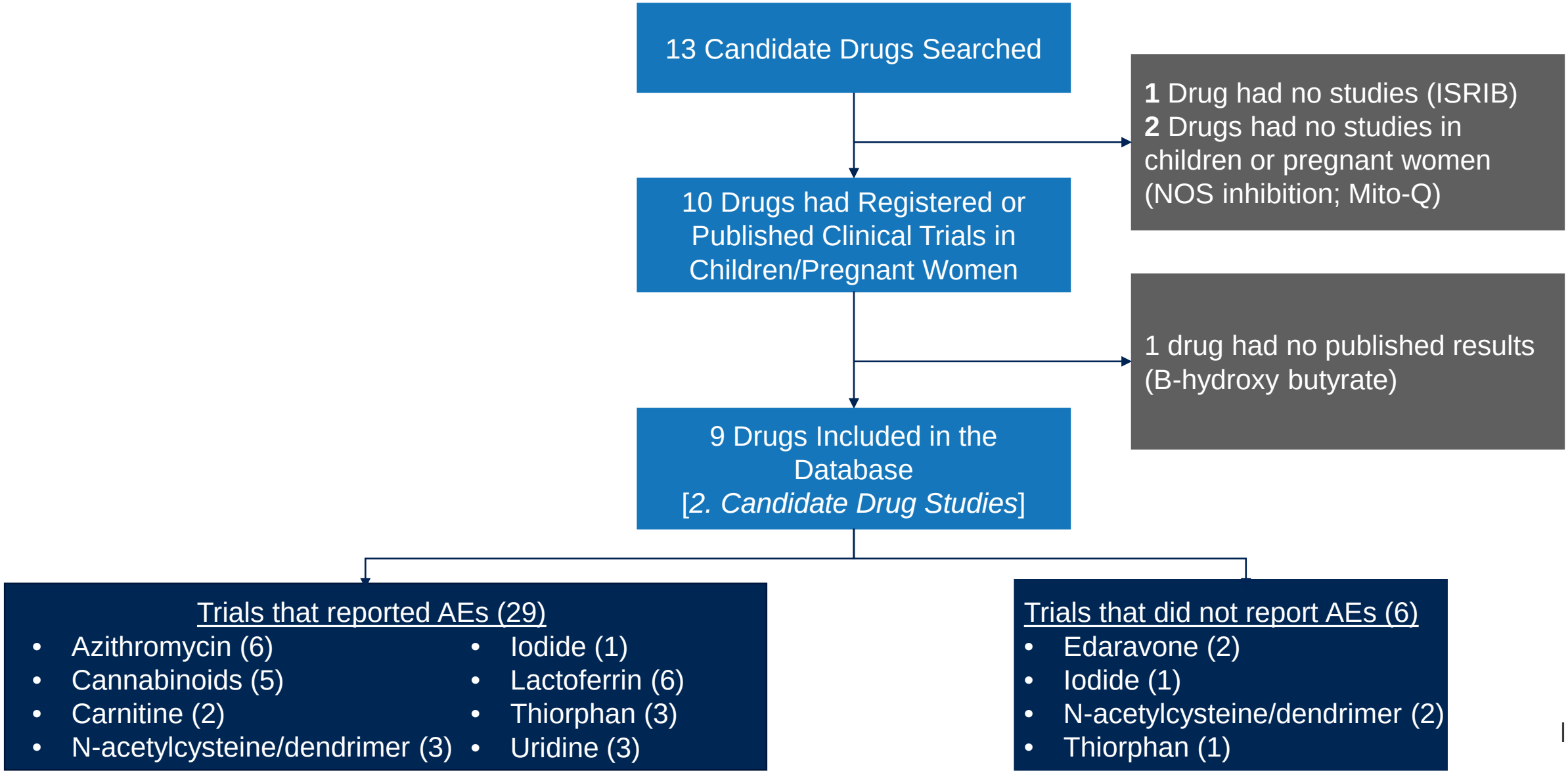
Drug	Group	NCT Number	Title	Acronym	Status	Study Results	Conditions	Interventions	Outcome Measures	Sponsor/Collaborators	Gender	Age	Phases	Enrollment	Funded Bys	Study Type
Azythrmoycin	Children	NCT02911935	Azithromycin to Prevent Whe	APW-RSV-II	Active, not recruit	No Results Availab	Respiratory Syncytial V	Drug: Oral azithro	The occurrence of a thirc	Washington University Scho	All	1 Month to 18 M	Phase 2|Ph	200	Other	Interventiona
Azythrmoycin	Children	NCT02047981	Mortality Reduction After Ora	MORDORIMort	Completed	No Results Availab	Childhood Mortality	Drug: Azithromycir	All-cause Mortality Rate	University of California, San	All	1 Month to 60 M	Phase 4	227000	Other	Interventiona
Azythrmoycin	Children	NCT03682653	Neonates and Azithromycin,	NAITRE	Recruiting	No Results Availab	Childhood Mortality	Drug: Azithromycir	6 month mortality - all ca	University of California, San	All	up to 27 Days Â	Phase 4	22000	Other	Interventiona
Azythrmoycin	Children	NCT02630394	A Pilot Study of Azithromycin Prophylaxis for Acute		Withdrawn	No Results Availab	Sickle Cell Disease|Ac	Drug: Azithromycir	Number of participants v	University of Mississippi Me	All	6 Years to 16 Ye	Phase 1	0	Other	Interventiona
Azythrmoycin	Children	NCT02414399	Azithromycin to Prevent Post-	Toto Bora	Recruiting	No Results Availab	Pneumonia|Diarrhea|	Drug: Azithromycir	Composite outcome of n	University of Washington|Ke	All	1 Month to 59 M	Phase 4	1400	Other|NIH	Interventiona
Azythrmoycin	Children	NCT03676764	Community Health Azithromy	CHAT	Not yet recruiting	No Results Availab	Childhood Mortality	Drug: Azithromycir	All-cause Mortality Rate	University of California, San	All	1 Month to 59 M	Phase 4	447780	Other	Interventiona
Azythrmoycin	Children	NCT01008761	Trial for the Treatment of Acute Asthma in Wheezy		Unknown status	No Results Availab	Asthma	Drug: Azithromycir	To determine if treatmei	Janielee Williamson|Unive	All	12 Months to 60	Not Applica	440	Other	Interventiona
Azythrmoycin	Children	NCT01486758	Azithromycin to Prevent Whe	APW-RSV	Completed	Has Results	RSV Bronchiolitis	Drug: Azithromycir	IL-8 Concentrations|Prop	Washington University Scho	All	1 Month to 18 M	Phase 2	40	Other	Interventiona
Azythrmoycin	Children	NCT02531984	The Efficacy of Azithromycin i	AZI-STOP	Unknown status	No Results Availab	Non Cystic Fibrosis Bro	Drug: Azithromycir	Time of onset of the firs	Assistance Publique Hopita	null	3 Years to 17 Ye	Phase 3	100	Other	Interventiona
Azythrmoycin	Children	NCT02003911	Azithromycin for Children Hospitalized With Asthm		Completed	No Results Availab	Asthma	Drug: Azithromycir	Length of Stay|Readmiss	Montefiore Medical Center	All	4 Years to 12 Ye	Phase 4	159	Other	Interventiona
Azythrmoycin	Children	NCT01778634	Trial of Intravenous Azithrom	AZIPIII	Active, not recruit	Has Results	Ureaplasma Infections	Drug: Azithromycir	Number of Participants \	University of Maryland|Euni	All	up to 72 Hours Á	Phase 2	121	Other|NIH	Interventiona
Azythrmoycin	Children	NCT03682640	Azithromycin Insulin Diet Int	AIDIT	Recruiting	No Results Availab	Diabetes Mellitus, Typ	Drug: Azithromycir	Stimulated C-peptide du	Uppsala University|GÃ¶teb	All	72 Months to 19	Phase 2	60	Other	Interventiona
Azythrmoycin	Children	NCT03485703	Azithromycin in the Prevention of Lung Injury in Pre		Completed	No Results Availab	Bronchopulmonary Dys	Drug: Azithromycir	bronchopulmonary dysp	Hospital de Clinicas de Port	All	up to 72 Hours Á	Phase 4	80	Other	Interventiona
Azythrmoycin	Children	NCT03338244	Mortality Reduction After Ora	MORDORIIMortY5	Recruiting	No Results Availab	Childhood Mortality	Drug: Azithromycir	All-cause Mortality Rate	University of California, San	All	1 Month to 60 M	Phase 4	227000	Other	Interventiona
Azythrmoycin	Children	NCT03854929	Ciprofloxacin Versus Azithron	CIPAZ	Not yet recruiting	No Results Availab	Dysentery, Shigella|Sh	Drug: Ciprofloxacii	Assess the Clinical treat	Oxford University Clinical Re	All	6 Months to 60 !	Phase 4	364	Other	Interventiona
Azythrmoycin	Children	NCT03568643	Azithromycin for Uncomplicated Severe Acute Malr		Not yet recruiting	No Results Availab	Uncomplicated Severe	Drug: Azithromycir	Nutritional recovery|Ma	University of California, San	All	6 Months to 59 !	Phase 4	200	Other	Interventiona
Azythrmoycin	Children	NCT02282176	TINN2: Treat Infection in Neo	TINN2	Withdrawn	No Results Availab	Bronchopulmonary Dys	Drug: Azithromycir	The proportion of survivi	Institut National de la Santé	All	23 Weeks to 28 '	Phase 3	0	Other|Industry	Interventiona
Azythrmoycin	Children	NCT00796224	Pharmacokinetics Of Azithromycin Immediate Rele		Completed	Has Results	Acute Otitis Media	Drug: 60 mg/kg azi	Area Under the Curve Fro	Pfizer	All	6 Months to 11 '	Phase 2	38	Industry	Interventiona
Azythrmoycin	Children	NCT01596894	Azithromycin Based Therapy for Induction of Remis		Completed	No Results Availab	Crohn's Disease	Drug: Azithromycir	Response rate at 8 week	Prof. Arie Levine|Wolfson M	All	5 Years to 17 Ye	Phase 4	73	Other	Interventiona
Azythrmoycin	Children	NCT02426112	Bronchopulmonary Function	BREATHE	Recruiting	No Results Availab	Chronic Lung Disease|	Drug: Azithromycir	Forced Expiratory Volum	London School of Hygiene a	All	6 Years to 16 Ye	Phase 3	400	Other	Interventiona
Azythrmoycin	Children	NCT00944515	Efficacy of Azithromycin Prophylaxis in Preventing R		Completed	No Results Availab	Sinusitis	Drug: placebo|Dru	frequence of acute sinus	Mahidol University	All	5 Years to 15 Ye	Not Applica	40	Other	Interventiona
Azythrmoycin	Children	NCT01919996	PASS Study To Evaluate The Potential Of Zithromax		Terminated	Has Results	Pharyngitis|Tonsillitis	Drug: Azithromycir	Occurrence of a Clinicall	Pfizer	All	12 Years to 17 Y	Phase 2	8	Industry	Interventiona
Azythrmoycin	Children	NCT00319956	Trial II of Lung Protection With Azithromycin in the		Completed	Has Results	Bronchopulmonary Dys	Drug: Azithromycir	Incidence of Bronchopul	Hubert Ballard|American Lu	All	up to 72 Hours Á	Phase 2	220	Other	Interventiona
Azythrmoycin	Children	NCT03676751	MORDOR II Burkina Faso: Lon	GAMIN	Not yet recruiting	No Results Availab	Child Growth|Diversity	Drug: Azithromycir	Intestinal microbial dive	University of California, San	All	up to 59 Months	Phase 4	450	Other	Interventiona
Azythrmoycin	Children	NCT02211729	A Trial of Seasonal Malaria C	SMCAZ	Completed	No Results Availab	Malaria|Respiratory Ir	Drug: Sulphadoxir	severe morbidity and mc	London School of Hygiene a	All	3 Months to 59 !	Phase 3	22090	Other	Interventiona
Azythrmoycin	Children	NCT02707523	Prospective Pilot Clinical Trial of Azithromycin Trea		Active, not recruit	No Results Availab	Respiratory Syncytial V	Drug: Azithromycir	Compare the mean seru	University of Alabama at Bir	All	up to 16 Years Â	Early Phase	48	Other	Interventiona
Azythrmoycin	Children	NCT01382004	Single-dose Azithromycin for the Treatment of Yaw		Completed	No Results Availab	Yaws|Treponema Infe	Drug: Penicillin-G	Serologic cure|clinical c	Lihir Medical Centre|Centre	All	6 Months to 15 '	Phase 3	255	Other	Interventiona
Azythrmoycin	Children	NCT02344628	Comparison of Two Different Doses of Azithromyci		Completed	Has Results	Yaws	Drug: Azithromycir	Number of Participants \	London School of Hygiene a	Male	6 Years to 16 Ye	Phase 3	583	Other|U.S. Fed	Interventiona
Azythrmoycin	Children	NCT00760279	An Open Label Evaluation of the Pharmacokinetics		Completed	No Results Availab	Ureaplasma|Bacterial	Drug: Azithromycir	Safety: Patients will be r	Eunice Kennedy Shriver Nati	All	up to 30 Days Â	Phase 1	16	NIH|Other	Interventiona
Azythrmoycin	Children	NCT00694694	Azithromycin + Artesunate v A	CAZAMS	Completed	No Results Availab	Malaria	Drug: azithromycir	Parasitological failure b	London School of Hygiene a	All	6 Months to 5 Y	Phase 3	261	Other	Interventiona
Azythrmoycin	Children	NCT03032042	Intestinal Microbiome Post-Azythromycin/Albenda		Unknown status	No Results Availab	Helminth Infection	Drug: Azithromycir	Microbial diversity in the	Francis I. Proctor Foundatior	All	up to 5 Years Â	Phase 4	100	Other	Interventiona
Azythrmoycin	Children	NCT00643149	A Multicenter, Randomized, Double-Blind, Double		Completed	No Results Availab	Tonsillitis	Drug: amoxicillin|	Bacteriologic response (	Pfizer	All	2 Years to 12 Ye	Phase 3	693	Industry	Interventiona
Azythrmoycin	Children	NCT01270074	Prevention of Bronchiectasis	COMBATCF	Recruiting	No Results Availab	Cystic Fibrosis|Bronchi	Drug: Azithromycir	Proportion of children w	Queensland Children's Med	All	6 Weeks to 6 M	Phase 3	130	Other	Interventiona
Azythrmoycin	Children	NCT00677833	Azithromycin Plus Chloroquine Versus Artemether-		Completed	Has Results	Malaria, Falciparum	Drug: Azithromycir	Percentage of Participan	Pfizer	All	6 Months to 12 '	Phase 2|Ph	361	Industry	Interventiona
Azythrmoycin	Children	NCT00643292	A Single, High-Dose Azithromycin Extended Releas		Completed	No Results Availab	Acute Otitis Media	Drug: amoxicillin/	clinical response (cure c	Pfizer	All	3 Months to 48 !	Phase 3	902	Industry	Interventiona
Azythrmoycin	Children	NCT00356720	Efficacy and Safety of 2 Dosing Regimens of T1225 I		Completed	No Results Availab	Trachoma	Drug: Azithromycir	Cure at end of study, i.e.	Laboratoires Thea	All	1 Year to 10 Yea	Phase 3	null	Industry	Interventiona
Azythrmoycin	Children	NCT01272635	Treatment of Preschool Child APRIL - OCELOT		Completed	Has Results	Asthma|Wheezing	Drug: Azithromycir	Progression to Clinically	Milton S. Hershey Medical C	All	12 Months to 71	Phase 3	607	Other|NIH	Interventiona
Azythrmoycin	Children	NCT00645112	A Comparison of Safety and Efficacy of Cefdinir Ora		Completed	No Results Availab	Acute Otitis Media	Drug: cefdinir (Om	Clinical cure rate at Eval	Abbott	All	6 Months to 6 Y	Phase 4	357	Industry	Interventiona

1. Intervention Effect Size | 2. Candidate Drug Trials | 3. Burden Estimate Studies | 4. Candidate Drug Database

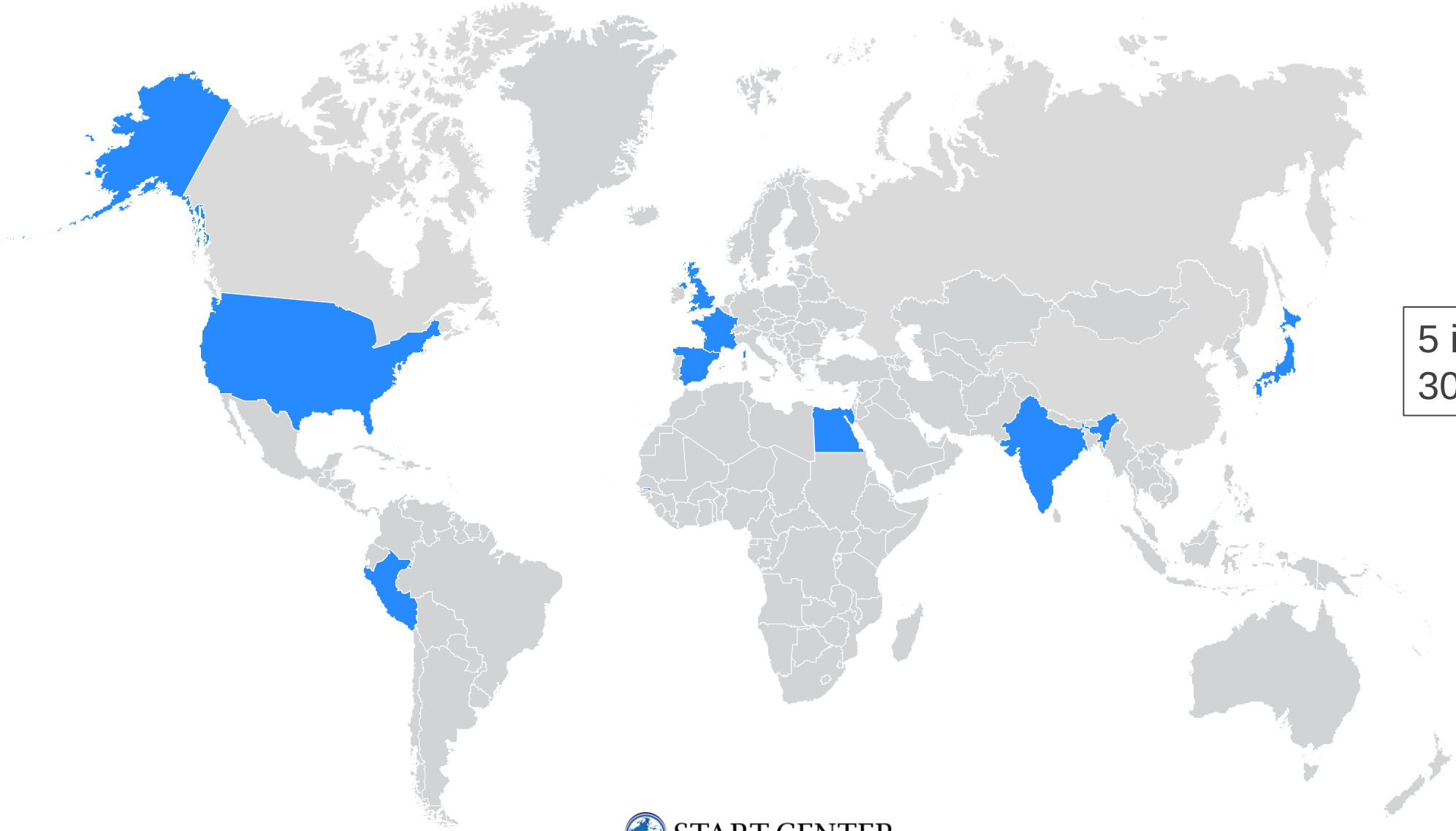
REGISTERED CLINICAL TRIALS IN TARGET POPULATIONS

Drug	Trials in Children (<18 years)	Trials in Neonates (<4 weeks old)	Trials in Pregnant Women
Azithromycin	186	6	32
B-hydroxy butyrate	18	0	4
Cannabinoids	22	1	4
Carnitine	55	6	17
Edaravone	1	0	0
Iodide	6	0	3
ISRIB	0	0	0
Lactoferrin	41	20	16
Mito-Q	0	0	0
N-acetylcysteine	71	1	16
Selective NOS Inhibition	0	0	0
Thirophan	4	0	0
Uridine	12	1	0
TOTAL	416	35	92

SELECTION OF STUDIES INCLUDED IN CANDIDATE DRUG STUDIES WORKSHEET



GEOGRAPHIC SCOPE OF CANDIDATE DRUG TRIALS



5 in LMICS
30 in HICs

HIGHLIGHTS

1. Lactoferrin, azithromycin and carnitine have the highest number of registered trials and published results in children and pregnant women
   - ↳ Minimal adverse events reported
2. Some evidence for possible drug related AEs in studies of N-acetylcysteine, iodide, and uridine
3. Most evidence for possible drug related AEs in studies of cannabinoids
4. No information for Mito-Q, ISRIB, selective NOS inhibition, B-hydroxy butyrate

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LIMITATIONS

- Targeted search only captures registered or published clinical trials
- Additional trials may exist in foreign clinical trial databases
- Several studies that are completed do not have published results
- Sample sizes in studies done in targeted populations are small, limiting their ability to capture less common adverse events.

DATASET SUMMARY

1. Intervention Effect Size
2. Candidate Drug Trials
3. Burden Estimate Studies
4. Candidate Drug Database

OPERATIONAL HIGHLIGHTS

- **Captures relative impact of HIE interventions** in LMICs & HICs *(Effect Size tab)*
- Serves as a living document that can be used to **prospectively collect data for future modeling** studies *(All tabs)*
- **Assesses the morbidities and prenatal mortality** attributable to HIE *(Effect Size & Burden Estimate tabs)*
- Supports **market assessment of potential neuroprotective and prophylactic agents** in target populations *(All tabs)*
- Details **clinical trial data for candidate drugs** that can be augmented as ongoing trials report findings *(Candidate Drug Trials & Database tabs)*

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QUESTIONS?

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