CODEBOOK

SAMPLE CREATION

R1

Jan 01 2013- Jan 01 2020

Sept 20

Alzheimer disease OR Alzheimer's disease OR AD OR Parkinson disease OR Parkinson's disease OR PD OR ALS OR Amyotrophic lateral sclerosis OR Huntington disease OR Huntington's disease

R2

Sept 26-Jan 01 2013- Jan 01 2020

MS (Multiple Sclerosis) OR MS OR Migraine OR Headache OR Epilepsy OR TBI OR Traumatic Brain Injury OR Stroke

R3

Sept 28

1. 01/01/2011-12/31/2012

Alzheimer disease OR Alzheimer's disease OR AD OR Parkinson disease OR Parkinson's disease OR PD OR ALS OR Amyotrophic lateral sclerosis OR Huntington disease OR Huntington's disease OR

MS (Multiple Sclerosis) OR MS OR Migraine OR Headache

1. 01/01/2011-12/31/2012

Epilepsy OR TBI OR Traumatic Brain Injury OR Stroke

1. 01/02/2020-01/01/2021

Alzheimer disease OR Alzheimer's disease OR AD OR Parkinson disease OR Parkinson's disease OR PD OR ALS OR Amyotrophic lateral sclerosis OR Huntington disease OR Huntington's disease OR MS (Multiple Sclerosis) OR MS OR Migraine OR Headache

<https://clinicaltrials.gov/ct2/download_studies?cond=Alzheimer+disease+OR+Alzheimer%27s+disease+OR+AD+OR+Parkinson+disease+OR+Parkinson%27s+disease+OR+PD+OR+ALS+OR+Amyotrophic+lateral+sclerosis+OR+Huntington+disease+OR+Huntington%27s+disease+OR+MS+%28Multiple+Sclerosis%29+OR+MS+OR+Migraine+OR+Headache&term=&type=Intr&rslt=&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&rsub=&strd_s=&strd_e=&prcd_s=01%2F02%2F2020&prcd_e=01%2F01%2F2021&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=>

01/02/2020-01/01/2021

Epilepsy OR TBI OR Traumatic Brain Injury OR Stroke

<https://clinicaltrials.gov/ct2/download_studies?cond=Epilepsy+OR+TBI+OR+Traumatic+Brain+Injury+OR+Stroke&term=&type=Intr&rslt=&age_v=&gndr=&intr=&titles=&outc=&spons=&lead=&id=&cntry=&state=&city=&dist=&locn=&phase=2&rsub=&strd_s=&strd_e=&prcd_s=01%2F02%2F2020&prcd_e=01%2F01%2F2021&sfpd_s=&sfpd_e=&rfpd_s=&rfpd_e=&lupd_s=&lupd_e=&sort=>

degen additional including the ones that were excluded from R1 that were excluded but should be included from new rules

R4

Later added indications- Rare diseases?

MESH terms added for all the above indications -any extra trials when expand search terms

CT.gov SEARCH PARAMETERS: Performed on DATE TBD

1. Condition or disease: Search terms as determined by the above method
2. Study type: “Interventional Studies (Clinical Trials)”
3. Status of recruitment: no restriction (looking for Actual primary completion dates, so likely mostly Completed/Terminated/Active not recruiting but completed- checked filtered results to see)
4. Phase: 3
5. Study start date: no restriction
6. Primary completion date: 01/01/2011-01/01/2021

SEMI-AUTOMATIC SCREENING (using excel filters)

1. Primary completion date: checked that type is “Actual” and not “Anticipated”
   1. Excluded, \*unless\* trial had an “Actual” overall completion date;
2. Intervention/Treatment: excluded if trial:
   1. Did not include at least one intervention that was classified as a “Drug” or “Biological” “ Dietary supplement” or “genetic” (“Other” and “combination product” is manually checked); ie exclude procedure or behavioral or device or radiation
   2. Included healthy volunteers;
3. Trial design: excluded if trial was labelled as:
   1. “Non-randomized” in randomization field;
   2. “Single group assignment” in “Model” field;
   3. 1 in “Arms” field;
4. Trial size: <30
5. Trial status: exclude if the trial recruitment status was:
   1. Withdrawn (i.e. no patients enrolled);
6. Indication: excluded if primary purpose is
   1. Diagnostic;
   2. Screening;
   3. Basic Science
7. Trial Location: exclude if the trial does not have a
   1. US or CAD UK, EU, Australia

**MANUAL SCREENING (Hannah and Robyn)**

1. Intervention check
   1. excluded if: surgery/behavioral/device intervention, extension, discontinuation studies, head to head or if there are more than two options for the experimental arm (ake “any anicogagulant) or if a phase 2, biosimilar against what it is biosimilar to, treating a second condition in our conditions (ie infection in PD patients)
2. Comparator
   1. must use a comparator that is either placebo or another treatment (as opposed to another dose of same drug, no historical controls
3. Indication
   1. check it is one of our included indications. Alzheimer's disease, Parkinson disease, Amyotrophic lateral sclerosis, Huntington's disease, Multiple sclerosis, Migraine, Headache, Epilepsy, TBI and Stroke (exclusively)
4. First Phase 3 trial: Overall, for a phase 3 trial to be included, it had to be the first phase 3 trial to investigate an experimental drug in a given population. We used TrialViewer1 to search for all earlier phase 3 trials of our experimental drug-of-interest. We used the following rules for determining if earlier phase 3 trials counted as evidence for the trial in our sample.

* Changes in the administration are not counted as prior evidence. Sample becomes first phase 3 investigating that drug condition or treating the same symptom in the same condition. If there is a previous trial with that drug in that indication treating a different symptom entirely-this is not prior evidence unless it looks at general outcomes too . Symptom trial can be proceeded by evidence investigating all disease outcomes general can be followed by symptom
* Basically, symptom trial can be preceded by general or other symptom trial as long as it looks at general-these count as prior evidence.
* Preclinical for any disease like CIS or people with AD mutation does not count only MCI or prodromal with probable diagnosis of AD or MS
* Prior evidence does not need to be exclusively in that indication
* Must be the first phase 3 trial for the treatment/indication pair registered on clinicaltrials.gov (unless there are phase 3 trials that are started within a year of each other and not completed):
* Prior evidence did not need to include all of the same symptoms-if it treated symptoms that were in the one in sample in that indication-prior evidence
* Prior evidence does not need to be exclusive
* If combination is not clear-but both are labeled adjuctive- they are prior evidence=cant tell the other drugs
* Phase 4 or 3 count as prior evidence
* Could be in control or exp arm just if it has been studied in a phase 3 trial in that indication before
* Pediatric can be evidence and other way around
* Same Day year before is earlier evidence

Search for publications

We will first us ClinicalTrials.gov when it has posted trial study results of the Phase 3 trials. Linked publications will then be verified for reference. For ClinicalTrials.gov records where no publication was linked, we will conduct Google Scholar and OVID searches to find study publications for each trial. The Google Scholar search will be done using NCT ID, Title (top-line & official), varying combinations of drug names, indication, and sponsor & investigator last name. The OVID search using MEDLINE and EMBASE will be done using a combination of the search terms: drug names from the experimental arm (any synonym of the drug mentioned in ClinicalTrials.gov should be included), and indication as listed in ClinicalTrials.gov , and “Clinical trial”, and “Phase 3”. If multiple publications/abstracts were found, the primary publication will be chosen (i.e. the publication that reports full primary-endpoint results). All trials will need to have a publication of their primary results to be included. For approved drugs without publications, drugs@FDA will be searched. Publications only containing interim results will not be used unless the study was terminated at interim analysis.

**Phase 2 to 3 Matching (Hannah, Karine,-for R1 /Robyn- for R2/3**

Find matches

To conduct the search for earlier phase trials, the introduction, conclusion, and research sections in the Phase 3 publications will be searched for P2 trials. If none meet the matching criteria (see below), we will search TrialViewer (ClinicalTrials.gov) for additional P2 trials. If there are still no matches, we will search for P2 trials using google scholar, MEDLINE and EMBASE via OVID

When confused:

* For approved drugs, drugs@FDA documents will be used to check that we correctly matched P2 trials to P3 trials.
* If the results are confusing, look for review articles on google scholar-sometimes they describe the translational timeline
* As a last resort, corresponding authors or sponsors will be emailed to query about possible phase 2 trials. Also look on regular internet for rules.

Determine if it is a match

To determine if a P2 trial was eligible to be a match, it must have a primary start date that is a year or more earlier than primary start date of the phase 3 study in our sample, as indicated by ClinicalTrials.gov (or the recruitment start date of the publication if registration date was unavailable) AND Match on

If cant tell date-if published in year of start date- give to them-otherwise no

1. Indication
   1. Phase 2 trials will only be considered a match to the phase 3 trial in our sample if it is in the same condition dont need to be specific (mild/moderate for now
2. Intervention
   1. Same drug or biologic
      1. A trial that investigates a drug/biologic as a monotherapy cannot be used as prior evidence for a trial that is investigating the same drug in combination therapy (and viceversa)
      2. If the one trial is x+any drug in this category and the other is x+one drug of that type-this is ok
      3. Change in formulation of the drug is not prior evidence

P2/3 are put into the preceeded category

If terminated with no data-it is not counted

Extension not counted

Positivity of Prior evidence

* Primary- copy the primary endpoints
* Note if it is clinical or biomarker endpoint or if it is safety or if it is both
* Positivity of primary as defined in the methods section- if there is a clinical endpoint-use that for positivity
  + If they diffined positivity using specific criteria we use that
  + If not and they separate into two groups and one is pos and the other is nonpos we give them the point-mark as positive -saw a positive signal
    - Especially when different dose groups could be only one pos group
* If it is not positive on primary clinical endpoint note if it was pos on a secondary
* Justification? Are they spinning it to be positive? Copy what they say?

Classification

* True bypass: No phase 2 trial in the drug and indication
* Ambiguous evidence: Will include times when there are multiple trials with conflicting results (not 2 priamry clinical trials-if one is positive we put into proceeded group), where a primary endpoint is negative, but a secondary is positive, or when subgroup analyses are used as the positive signal. Mark this as a one if there is a p2 trial in the drug/indication but it does not have a primary clinical efficacy endpoint and be positive on that endpoint based on what was pre-specified in the trial. Futility trials are in this category? Authors opinion taken goes here too. When pos on biomarker signals/efficacy signals in the P2 but primary was not efficacy
* Proceeded by positive P2 trial: To be deemed positive, P2 trials must have a primary clinical efficacy endpoint and be positive on that endpoint based on what was pre-specified in the trial.
  + Trials that were positive after stopping for futility were also put into this category.

**Extraction (Hannah, Maya)**- definitions in the codebook in form

* Termination status
* Published within a year of start date is ok too ie Feb 2006 and ours is Jan 2007
* Symptom
  + Does it treat a symptom of the condition
    - Include only if it is widely used as measure of disease modification of the condition (as determined by consultation with neurologists)
    - If not exclude
    - Make list to send and move these forward in the meantime
    - Dyskinesia is not a symptom for our purposes
* Positivity status-positive on a primary outcome
  + Trials with multiple primary outcomes were considered positive if one of them was positive. We looked at p-values and the definition of positivity in the statistical analysis section to determine trial positivity.
  + Negative trials were significantly worse off in the experimental arm.
  + If any primary endpoints were were positive or negative they are classified as such
    - Idk abt this
* Picking the highest dose arm only applies to the following two thingsor most often if same dose-not positivity
  + SMD-
    - for those with two doses-take the one that is first for hierarchical testing if there truly is not one higher priority take higher and mark it. Adas cog wins over others for SMD – for which data is available
    - Only taken when it is a primary
    - Take adjusted pvalue if available
  + WdueAE
    - From ct.gov or consort documents
    - Paper priority
* Approval status
  + if not fda regulated-put approved not seeking approval
  + If change in delivery of drug-approval of first kind of delivery is the first date used
  + Doesn’t need to be in that indication
  + Important bc it tells u if it is approved in new indication or new formulation
* Funding (industry vs nonindustry). -if no funder available take sponsor-assume they funded
  + Any pharma involvement=pharma
* Check for inclusion-Exclude CHECK ALL OF THESE expecially phjase 2/3 and paper not correct
  + Trial Location: exclude if the trial does not have a
    - US or CAD, EU, UK, Australian research site.
  + Not head to head
  + Primary efficacy endpoint
  + Phase 2/3 exclude
    - If it is labeled as a phase 2/3 in the ct.gov record, but the paper is labeled a phase 2 study-we will exclude
    - If it is labeled as a phase 2/3 in the ct.gov record but the paper has no phase label we will include-assume it is p3
  + Paper is not right
* If more than one arm was included as primary analysis, they were both included and considered separately in the analyses
  + 2 comparators do not count as two arms.

TASKS green=both me and Ras yellow-for me

OVER BREAK

Me-B4 break

* Email collabs

OVER BREAK

* Define indications
  + Orphan disease or non orphan disease -prevalence
  + Severe disease or non severe disease (operationalized based on 5-year mortality or disability)-severity (prognosis)
* Data check
  + SMDs negatives are in the right direction
  + check p3 positivity-giving them the point even if they didn’t define that as positive?
    - Only need to check positive ones
    - Change this—make only ones defined as positive-positive
    - What if done and positivity don’t line up aren’t in the same group
  + Check adjuvant matches with old ones that found an earlier p3
    - ones that didn’t have a earlier phase 3 all good
* Methods- Supplement
* Coding/analysis plan/clean data
* Screen R4

Maya & Robyn

* Approval Status
* Search for P3s that don’t have primaries again

Robyn-

* Earlier P3 check
* Screen R4s

WHEN BACK

* C1 with textbook
* Publications
  + Email authors where you didn’t find pubs
* P2/3
  + Define what a p2 is and what a p3 is
  + Define the p2/3 ones in our sample as p3 or excludes
    - Email authors to see if they moved on to p3
  + Define the p1/p2/p3 ones in the matching
    - Modify it in puttogether
* True Bypass further search-with Robyn/Maya
  + MEDLINE and EMBASE via OVID-only do once I define p2/3
* R4-MESH terms/extras from R3
  + - [NCT00340834](https://clinicaltrials.gov/show/NCT00340834)did not download into R3?
* Include/extract from included ones
* CONSORT
* Send NCTs to murph to get trial duration and number of patients from P2 trials-p3 dates
  + Extract from ones without NCT

Questions 4 collabs/JK

* Collabs
  + Go through subgroups and pediatrics in matching document-state you want to make broader rule because of screening
  + added indications- Rare diseases?
  + Symptoms
    - AD-insomnia, agitation, apathy
    - Huntingtons-chorea
    - Stroke- fatigue, walking deficits
    - MS- Chronic Visual Loss Related to Optic Neuritis, Processing speed, pain
    - PD-sleepiness
    - TBI-mood disorders
* JK
  + Conflicting positivity 2 clinicals-give the preceeded point I think
  + NA withdrawls--mean there were 0- can we assume not reporting is 0 in consort diagram
  + phase 2 that did not analyze efficacy as ambigious
  + Should I use P2 portion of P2/3 to count as prior evidence?
* Murph
  + MESH terms added for all the above indications -any extra trials when expand search terms

FOR THE PAPER

<https://journals.lww.com/neurotodayonline/fulltext/2015/09030/NEWS_FROM_THE_ALZHEIMER_S_ASSOCIATION.6.aspx?casa_token=G8S79pHqaqoAAAAA:ZawunakDBKnA91wcmvnFELAa0-ivjuPMSbcrrzOk2Bz-e7NBtLOi0vT6-2HMRBzV0V8n0Se54Sa8iimNRz8YDCOuZ53F>

biomarker sensitivity analysis?? What if indication doesn’t have clinical outcomes