

Recruiting for MS Trials

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Framing the problem

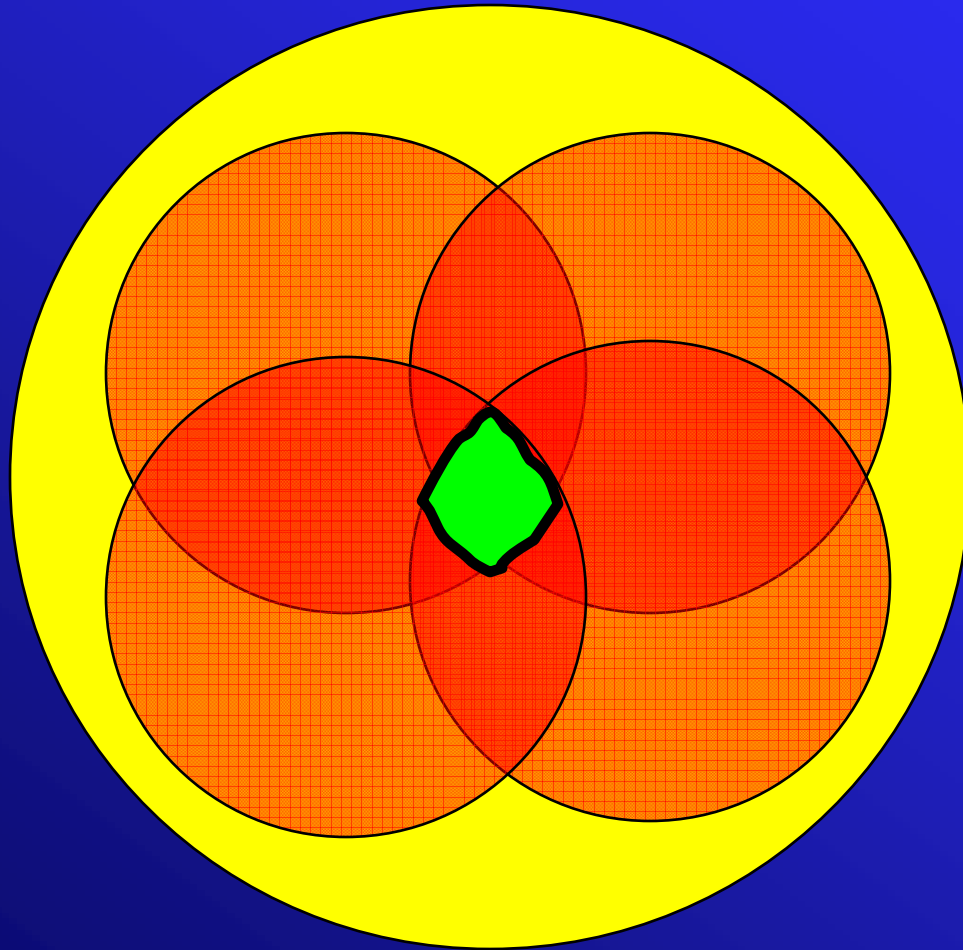
- We have a large number of potential treatments to test in MS patients.
- Pre-clinical studies don't adequately predict which treatments are most promising.
- There aren't enough patients (or money or time) to study everything
- Unrealistic recruitment expectations can be extremely expensive

**Investigators always
overestimate subject
availability**

Why is there a problem?

- Limited # of MS patients
- Limited # of investigators
- Many patients prefer being treated according to emerging standards of care
- Restrictive eligibility criteria

Issue #1: Restrictive eligibility criteria



An example

- Aricept, 1999
 - Goal: 20 sites, 12 patients/site in 1 yr
 - Result: 20 sites, 40 patients in 1 yr
 - Reason: competing eligibility criteria
 - ❖ Severe cognitive impairment
 - ❖ Ambulatory
 - ❖ Community-dwelling
 - ❖ No anticholinergics, anti-spasticity agents, anti-convulsants, etc.

Another example

- CAMPATH, 2003
 - MS symptoms < 3 yrs
 - At least 3 attacks
 - EDSS < 3
 - Never treated
 - Gd+ MRI at screening

Issue #2: relatively unappealing treatment

- Inconvenient
 - Self-injections > other injections > oral
- Bypasses perceived standard of care
 - Placebo
 - Anything new for RR, CIS?
- Safety issues

Relatively unappealing treatment

- ACT, 2004
 - Patients with recent attack or Gd+ on Avonex
 - Add oral methotrexate or IVMP
 - Many patients did not want steroids
 - Patients wanted Tysabri instead

Other examples

- Combi-Rx?
 - Avonex vs Copaxone vs both for RRMS
 - 8 self-injections/week
- Lipitor?
 - Lipitor vs placebo for CIS
 - Both bypass the perceived standard of care

Issue #3: relatively unappealing trial

- Too many evaluations
 - Relative to standard care
- Unpleasant evaluations
 - LPs
 - MRIs
 - Anything invasive or unfamiliar

An example

- Upcoming trial
 - Eye exams every 6 months, including eval by Ophthalmologist, field testing, OCT
 - Full derm exam every 6 months
 - Formal PFTs every 6 months

Issue #4: Wrong sites

Study population:

- CIS
- Untreated MS
- Breakthrough disease
- Symptomatic therapy

Site needs:

- Optic neuritis
- New diagnoses
- Treated patients
- Long-term patients

Solutions

- More sites
- Improve access to patients
- Improve study design

Improve access to patients

- Simple recruitment methods
 - Site practices
 - Word of mouth
- Advertise to patients
 - Local – newspaper, radio, TV
 - ❖ Paid or press-release
 - Study-wide
 - ❖ Internet – NMSS, etc.
 - ❖ Registries – NMSS, clinicaltrials.gov, centerwatch.com
- Advertise to colleagues
 - Letters, brochures, posters, meetings
 - Internet, registries

Improve study design

- Minimize eligibility restrictions
- Minimize unpleasant evaluations
- Choose appealing treatment arms
 - Appealing administration
 - Understandable mechanism of action
 - Exciting preliminary data
 - Minimal safety concerns
- Avoid placebo comparator if possible

Alternatives to placebo

- Active comparator
 - Superiority
 - Non-inferiority (equivalence)
- Dose-ranging
- Delayed start
- More flexibility in Phase II than Phase III

Will we succeed with recruiting for this trial?

Question #1: Is this trial worth doing? (Does the trial address an important unanswered question?)

Competing interests

- Recruitment will work best when the investigator can sell the treatment,
- but, the study and all other alternatives must be presented with appropriate balance,
- so, the investigator should sell the trial, not the treatment.

Equipoise

- A legitimate state of uncertainty regarding the advantages of one approach over another.
- The goal of any clinical trial is to shift away from equipoise.

Is this trial worth doing?

- Equipoise exists between study arms
- Design will shift equipoise
- Shifting equipoise is important

**Will we succeed with
recruiting for this trial?**

Question #2: Do we have access to
the right patients?

**Will we succeed with
recruiting for this trial?**

Question #3: Can we improve
access to the right patients?

**Will we succeed with
recruiting for this trial?**

Question #4: Will the right patients
be interested in participating?

Solutions

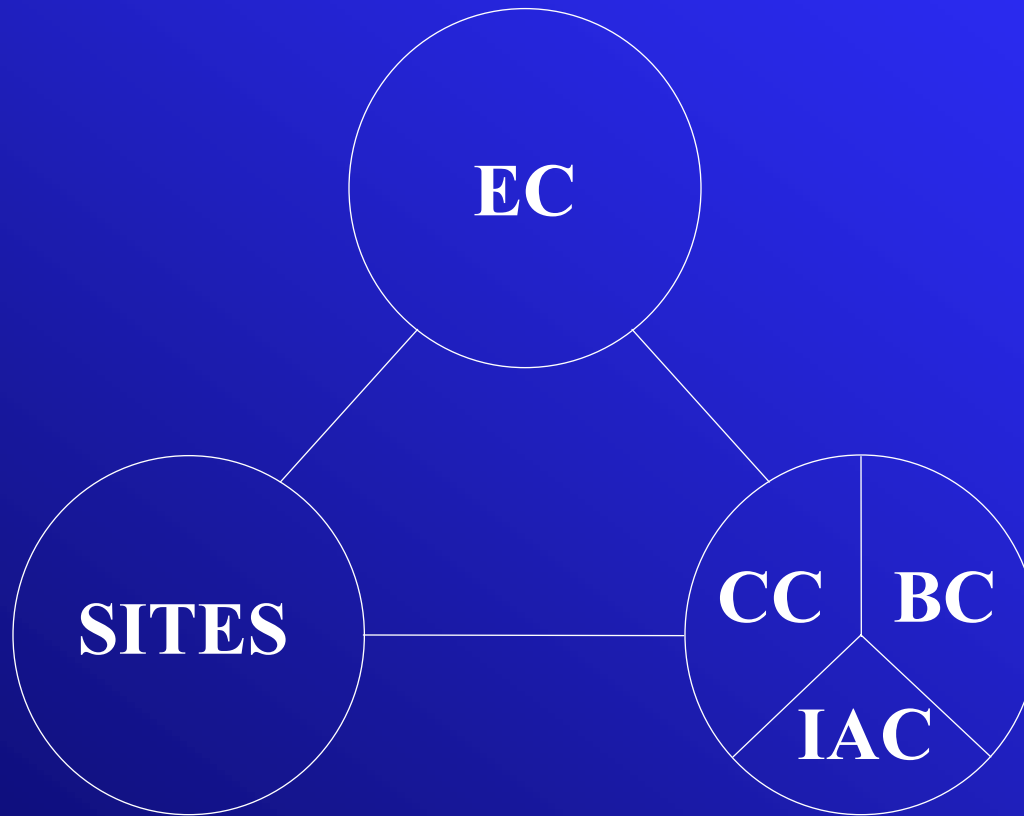
- More sites
- Improve access to patients
- Improve study design

- Better integration of investigators and coordinators into study planning and implementation

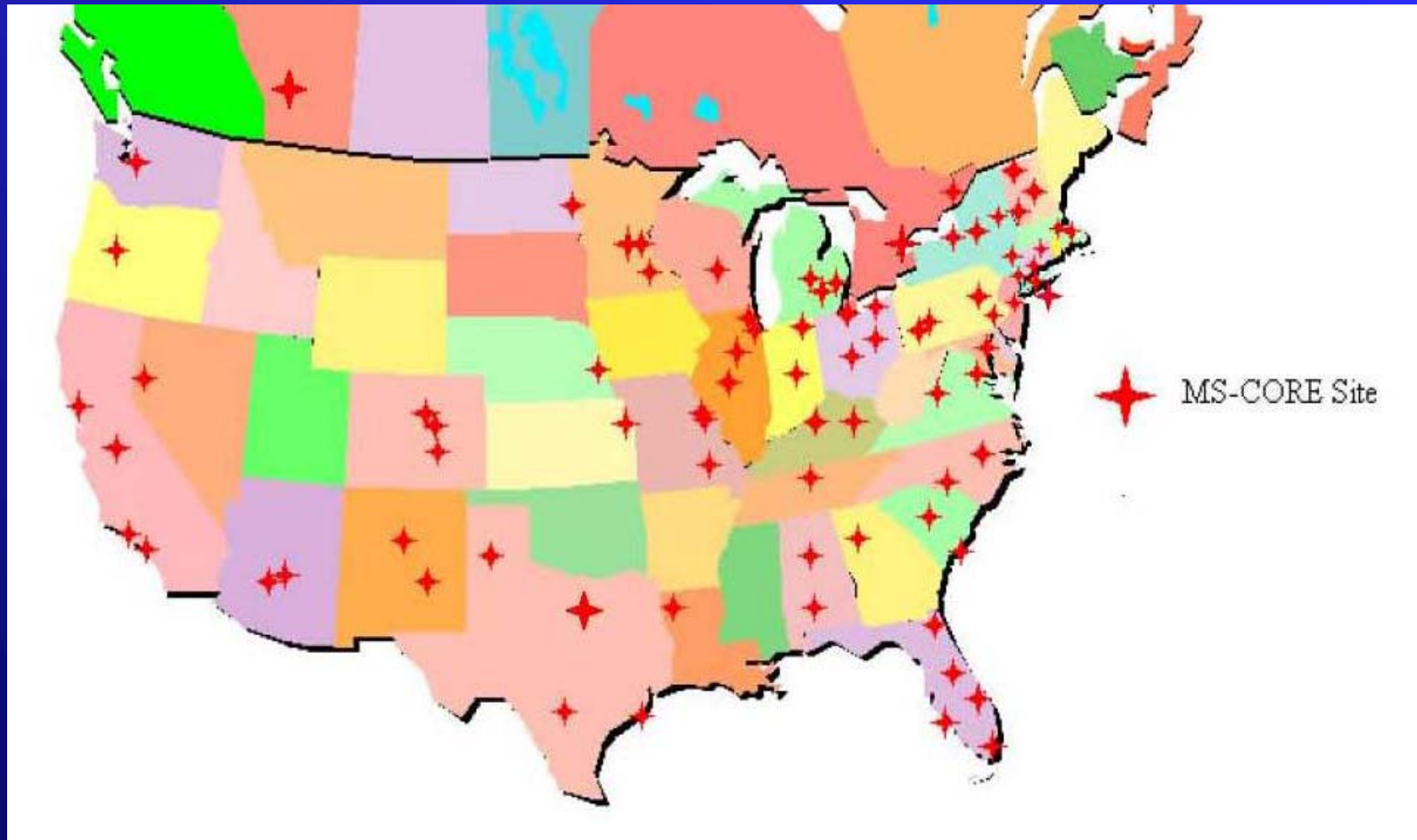
MS-CORE

- MS Cooperative Research Group
- Sponsored by the NMSS in 2003
- A consortium of investigators committed to:
 - cooperative planning, implementation, analysis, and reporting of multicenter clinical research
 - full and open scientific communication
 - peer review
 - full disclosure of potential conflicts of interest
 - democratic governance

MS-CORE organization



MS-CORE sites



MS-CORE activities

- MSFC refinement
 - Awaiting results from natalizumab studies
- Developed phase II development plan for an oral CD4 antagonist
 - Project on hold by company
- Developed plan for a study of estriol for relapse prevention in post-partum women
 - Still negotiating with company

MS-CORE activities

- Neuroprotective Pilot Working Group
 - Applied for multicenter randomized controlled pilot study of minocycline to NINDS – not funded
 - Applied for multicenter cross-sectional reliability study to NMSS – reviews pending
 - Planning a multicenter longitudinal study to determine optimal endpoints