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Boosting Enrollment in Clinical Trials: Validation of a Regional Network Model

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Abstract

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BACKGROUND—Clinical trials of stroke therapy have been hampered by slow rates of enrollment.

PURPOSE—Our purpose is to validate a previously-developed model for accelerating enrollment in clinical trials by replicating it at new locations. The model employs coordinators who travel from a host institution to enroll participants from a network of participating hospitals. Active surveillance assures identification of all eligible patients.

METHODS—Among 70 US investigators participating in an NIH-funded trial of stroke prevention, five investigators were invited to develop local identification and outreach networks (LIONs). Each LION comprised a LION coordinating center servicing multiple hospitals. Hospitals provided names of patients with stroke or TIA to researchers at the LION coordinating center who initiated contact; patients were offered home visits for consent and randomization. Outcomes were feasibility, enrollment, data quality and cost.

RESULTS—Five LIONs varied in size from 2 to 8 hospitals. All 24 hospitals we approached agreed to participate. The average monthly rate of enrollment at the research sites increased from 1.4 participants to 3.5 after expanding from a single institution model to the LION format (mean change=2.1, range 0.9-3.7). Monthly performance improved over time. Data quality was similar for LIONs and non-LION sites, except for drug adherence which was lower at LIONs. The average cost to randomize and follow one participant during the study interval was 2.4 times the cost under the per-patient, cost-reimbursement strategy at non-LION sites. The cost ratio declined from 3.4 in year one to 1.8 in year two.

LIMITATIONS—The LION strategy requires unprecedented collaboration and trust among institutions. Applicability beyond stroke requires confirmation.

CONCLUSION—LIONs are a practical, reproducible method to increase enrollment in trial research. Twelve months were required for the average site to reach its potential. The per-participant cost at LIONs was higher than conventional sites, but declined over time.

INTRODUCTION

Many recent randomized clinical trials (RCTs) of stroke therapy have been hampered by slow participant accrual causing delayed completion and increased cost(1-4). To improve the rate of recruitment in RCTs of therapies for secondary prevention of stroke, we recently described a novel collaboration among several hospitals in Connecticut(5) that was successful in recruiting participants into the Insulin Resistance Intervention after Stroke (IRIS) Trial (NCT 00091949). The distinct feature of this collaboration is employment of research coordinators at a host institution, in this case a medical school, who travel to enroll participants from a network of participating hospitals. Coordinators actively survey each hospital, usually by reviewing electronic lists of patients with the diagnosis of stroke or TIA, to identify all patients who may be eligible for the trial. Most of the direct contact with patients occurs in their homes as a result of outreach strategies designed to lower barriers to research participation.

We refer to this collaboration of hospitals as a Local Identification and Outreach Network (LION). The LION in Connecticut comprised local hospitals served by a LION coordinating center located at the Yale School of Medicine. The LION coordinating center provided the base for traveling coordinators, other research associates, and the investigators who constructed and maintained the LION.

The Connecticut LION enrolled participants at nine times the rate of more typical single hospital sites in the IRIS trial and achieved comparable data quality. The success of the Connecticut LION required intensive coordination among hospitals for research logistics

and a willingness on the part of all participating hospitals to delegate key responsibilities to the LION coordinating center for the ethical, humanistic conduct of research.

This paper reports the results of an effort to validate the LION strategy by showing that the performance in Connecticut can be replicated in LIONs established elsewhere.

METHODS

LION Assembly in Each Geographic Area

One year after initiation of recruitment into the IRIS trial, we invited six investigators from one-hospital sites to create multiple-hospital LIONs. Five accepted. The investigators were selected on the basis of strong recruitment performance during the first year of the IRIS trial and their location at institutions within a practical commute of multiple hospitals. Investigators created LIONs in Boston, Massachusetts; Cincinnati, Ohio; Jacksonville, Florida; Mobile, Alabama; and Portland, Oregon. The number of hospitals and neurology practices in each LION was determined by the original goal for each LION to randomize four participants each month within six months of operation. From prior surveys of IRIS sites, we estimated that 100 patients discharged alive with ischemic stroke or TIA would need to be identified to randomize four, and that each LION would need to put 3000 hospital beds (or about 5 moderately large hospitals) under active surveillance to identify 100 patients. In addition to an adequate network of hospitals, each LION was required to 1) identify a local LION coordinating center to handle administrative duties, host the coordinators, and store data, 2) assure that each hospital or practice was sufficiently close to the LION coordinating center to permit servicing by the center's personnel, 3) identify a physician at each hospital or practice to serve as site principal investigator, and 4) obtain approval from the Institutional Review Board (IRB) of each hospital or practice for the LION protocol for active surveillance, enrollment, and follow-up.

Recruitment Protocol for LIONs

We petitioned the IRB at each hospital or practice for permission to use active surveillance(5). Active surveillance was defined as any system for identifying and contacting every patient within a health system who might be eligible for the IRIS trial. In our preferred strategy, staff from the local LION coordinating center had access to admission or discharge logs for patients with ischemic stroke and transient ischemic attack (TIA). If this strategy was not accepted by the governing IRB, we negotiated an alternative. Identification of patients by clinicians or other health care workers during routine care with subsequent referral to the LION coordinating center was not considered active surveillance unless those clinicians or workers were part of the research team and routinely saw every patient with stroke and TIA at their hospital or practice. Active surveillance required a waiver of HIPAA research authorization except when researchers were the care providers(6).

Once a potentially eligible patient was identified, a research associate from the local LION coordinating center reviewed the medical records, if available, to confirm initial eligibility. Remote review of electronic records was preferred. If eligibility was not ruled out by this review, a research associate or an IRIS investigator obtained permission from an attending or personal physician to contact the patient.

If permission was granted, a research associate contacted the patient to complete more detailed eligibility screening. Eligible patients were invited to learn more during an in-person visit by a research coordinator who often traveled to the patient's home.

During the in-person visit, the coordinator explained the IRIS protocol, invited questions, and re-confirmed eligibility. Each eligible, willing patient signed two forms: a Research Authorization granting access to protected health information and an informed consent document covering blood testing for determination of eligibility and randomization, if eligible. Blood was then drawn (often in the home). Further enrollment activities and randomization were completed during subsequent visits(5).

Recruitment Protocols at IRIS Sites Other Than LION Sites

Outside the LIONs, site investigators typically recruited from one hospital(5). Site investigators were encouraged, but not required, to use active surveillance as described above. Coordinators outside the LIONs rarely performed home visits, and typically worked on more than one study. The main differences between the LIONs and other sites, therefore, were that LION coordinators covered multiple hospitals, worked exclusively or primarily on the IRIS trial, routinely made first contact with patients by telephone, and enrolled patients during home visits.

IRIS Protocol

Essential eligibility criteria include a TIA or ischemic stroke within 6 months, age over 39 years, absence of diabetes, ability to provide informed consent, and insulin resistance as determined by a fasting blood test(5). Eligible participants are randomized to placebo or pioglitazone. Surveillance for safety and outcome events is completed during regular telephone calls and annual in-person visits. Patients remain on study drug for up to five years. The primary outcome is time to stroke or myocardial infarction.

Data Management and Analysis

For this report, we included data on the five LIONs outside Connecticut. Performance data from each LION were compared with data at the host institution before its LION was created. In addition, we compared performance data from all LION sites combined (excluding the Connecticut LION) with non-LION sites during the same secular interval.

Data from LION and non-LION sites were handled the same. Data were collected on paper forms and converted to electronic format using Cardiff TeleForm ® v.10.1 software (Vista, California). Staff at the IRIS Trial Clinical Coordinating Center performed quality checks and resolved data queries. Data were analyzed using SAS Statistical software (v.9.1; Cary, North Carolina). Electronic data were stored in files created with Microsoft® Office Access 2003.

The co-primary, pre-defined outcomes were administrative feasibility and enrollment performance. Administrative feasibility was defined by recruitment of enough local hospital beds to achieve pre-specified goals for stroke discharges and participant enrollment, and receipt of local IRB approvals for active surveillance. As described above, we estimated that 3000 hospital beds or 100 discharges per month for ischemic stroke or TIA would be required to reach enrollment goals. The initial enrollment goal was to randomize at least four participants per month at each LION. This was changed after one year to a goal of 5.5 screening blood draws per month in recognition of the fact that sites could not control the proportion of participants who would screen eligible by the blood test.

The main secondary outcomes were cost and data quality. Recruitment and follow-up costs for each LION were calculated as total cost from the start of funding to 6/30/09. Each LION received funding for start-up activities lasting 6-9 months. We compared funds actually disbursed during the start-up and active recruitment phases with funds each site would have received under a strict cost-reimbursement strategy for activities actually completed during

the active recruitment phase ending 6/30/09. Funds provided to each LION coordinating center covered salaries for personnel, staff and participant travel costs within each network, IRB fees, pharmacy fees, research supplies, and facilities and administration fees. Each LION coordinating center was allowed to invoice for one full-time research associate during start up and two during the active recruitment phase, a physician-investigator (25% effort first year, then 20%), and an administrative assistant (15% effort).

Data quality was measured by compliance with the study protocol (e.g., proportion of required annual participant interviews completed). Adherence to the study drug was estimated by pill counts on bottles distributed during the study period. A participant was classified as having good adherence if he or she took at least 80% of protocol-prescribed pills.

RESULTS

Administrative Feasibility

We filed applications with 13 IRBs seeking approval to conduct research at 24 hospitals and 4 practices. No applications were denied. Based on these IRB approvals, the five LIONs each comprised 2 to 8 acute care hospitals and 0-4 neurology practices (Table 1). None of the networks reached the administrative goal of 3000 acute care beds under surveillance, but two LIONs reached or approached the alternative goal of 100 discharges per month for patients surviving an acute ischemic stroke or TIA.

Active surveillance was approved by all 13 IRBs for all 24 hospitals. Twenty hospitals provided scheduled electronic admission or discharge logs to the network coordinating center. Two hospitals approved a surveillance clinician who tracked admissions for stroke or TIA and reported them to the local LION coordinating center. At two hospitals, all staff neurologists were IRIS investigators and completed surveillance personally.

20/24 hospitals allowed coordinators to make first contact with all patients, but most required prior permission from a personal physician. Two would only allow coordinators to contact patients directly if they had registered willingness to be considered for research when approached in the hospital for participation in a stroke registry. If they were not in the registry, they could only be contacted after a treating physician secured their permission. At the four hospitals which would not allow coordinators to make first contact, a member of the clinical team had to make first contact to secure permission for a coordinator to call.

Enrollment Performance

Performance data for each LION are reported in Table 2. Across all sites, the average number of monthly blood screenings increased from 1.4 before the LION project to 3.5 after. There was substantial variability among sites, however, with an observed range in increments from 0.9 screenings per month to 3.7. Based on average performance over two years, only one site reached the revised goal of 5.5 screenings per month. A time trend analysis (data not shown) indicates that average performance among the LIONs increased until the fourth quarter when it reached and remained at about 65 screens per quarter. During the interval of the LION project, we observed no increment in average monthly rates for screening at non-LION sites.

Table 3 displays demographic and clinical characteristics of patients enrolled at the LIONs compared with other sites in the IRIS network; the groups are similar with respect to all features except history of myocardial infarction which was more common among participants from LIONs.

Experience with Outreach

Screening and randomization activities were performed primarily in participants' homes at four of the five LIONs. At the fifth LION (site 5), all patients were seen in a hospital-based neurology clinic. Despite frequent travel for participant interviews and phlebotomy, LION coordinators experienced no significant threats to their personal safety (e.g., crime, car accidents, needle sticks).

Data Quality

The quality of data obtained from LIONs was comparable to non-LION sites with the exception of adherence to the study drug which was lower for the LION participants (Table 4). Only 52% of participants from LIONs were classified as having good adherence compared with 66% of participants at other sites. The rates of good adherence for participants enrolled at LIONs 1-5 were 47%, 54%, 57%, 40%, and 55%, respectively.

Cost

The average total cost to randomize and follow one participant during the phase of active recruitment (7/1/07 to 6/30/09 for most sites), including start-up costs before enrollment started, was 2.4 times the cost that would be expected under a cost-reimbursement schedule ($13,555 compared with $5,539). This multiplier varied from 1.7 to 3.8 among the five sites. Excluding the start-up phase, the multiplier declined from 3.4 in year one to 1.8 in year two (average = 2.1 for both years).

Patient Acceptance of the LION Strategy

Among more than 500 direct contacts with patients, none filed complaints against the trial with member institutions or their IRBs. A few patients questioned how they were identified, but the answers satisfied their concerns about due protection for privacy.

DISCUSSION

Our findings confirm that the LION approach can improve enrollment in clinical trials for stroke. We assembled geographic networks of collaborating hospitals in five regions of the United States, each working under a common protocol for trial recruitment that included centralized research administration, active surveillance, and patient outreach. These five LIONs increased their average rate of enrollment in the IRIS trial by over 100%, from 1.4 participants per month to 3.5. During the two-year study period, the five LIONs enrolled for blood screening 27% (413/1513) of all patients enrolled for screening from 91 active sites in the IRIS trial.

Implementation of the LION protocol required approval by an IRB at each participating hospital. Use of a central IRB for all hospitals would simplify and improve future LIONs(7). However, the LION model may require a hospital to disclose protected health information (i.e., name, date of admission, contact information) to researchers from another institution. Hospitals are understandably cautious about such disclosure and often mandate changes to systems proposed by investigators. Until this area of research administration evolves and standard disclosure practices are more broadly accepted, hospitals may want to review and approve specific disclosure plans despite the central IRB. In our validation study, each hospital ultimately approved release of protected health information but not always according to our preferred method. In particular, some hospitals required an intermediary who first examined protected health information, and not every hospital allowed our researchers to make first contact with patients.

The LION model is distinct from other research networks in employing coordinators to travel to regional hospitals for purposes of participant identification, enrollment, and follow-up. This distinct model allows tight control over protocol implementation and collaboration with hospitals that may not traditionally participate in research. It could be adopted for research in any field and it could be adopted for acute care, provided network hospitals could implement the intervention. Unlike other network models, a LION is limited by the distance a coordinator can reasonably travel and the regional concentration of hospitals or practices. The LION model, which might be called an "outreach" or "commando" model, has previously been used by our group(8) and by investigators in Cincinnati(9, 10).

We are not aware of a published taxonomy of trial networks, but have proposed one in Table 5. Of the five listed models, the most well known is probably the "Managed Disease Community" model as exemplified by the Cancer Clinical Trials Cooperative Groups funded by the US National Cancer Institute(NCI)(11, 12). The NCI funds 10 regional groups each with a clinical coordinating center (sometimes called an operations center), a data center, and personnel at participating cancer centers who are poised to enroll participants into trials. Trial concepts are usually developed by investigators within the group, but approved and funded by the NCI. Unlike the Outreach model, each cancer center has its own in-house research team, including coordinators. The coordinating and data centers receive constant funding, but center teams are funded primarily when they enroll a patient in a trial. Similar networks with federally funded infrastructures have been developed by other NIH institutes, including Allergy and Infectious Diseases (NIAID) and Neurological Disorders and Stroke (NINDS). The Neurological Emergencies Treatment Trial sponsored by the NINDS implements trials that emerge from investigators outside the NINDS and pass peer-review(13). Unlike the NCI, NIAID, or NINDS Groups, the Outreach model has no on-going financial support; as described in this paper and used elsewhere, the outreach model is simply a tool to be used as a stand-alone network or within other trial networks.

A novel type of network, not categorized in table 5, includes pre-hospital responders. In Los Angeles, investigators have teamed up with emergency crews and 46 acute receiving hospitals to permit pre-hospital enrollment in an acute stroke trial(14). In Georgia, a regional telemedicine consultation system has been used to identify patients who can be rapidly enrolled or transported to a research hub for trial enrollment(15).

Although the LION sites in this validation project succeeded in substantially increasing IRIS enrollment, their performance fell short of pre-specified goals in some areas. Only two of the five LIONs assembled networks large enough to reach the goal of 3000 acute care beds or 100 age-eligible patients with TIA or ischemic stroke per month. Only one site reached the goal of 5.5 screening blood tests per month. These shortfalls are notable, but they do not negate the achievements of those LIONs that increased their enrollment activity with small networks.

In one area, adherence with the study drug, data quality was deficient for LIONs sites compared with non-LION sites. Potential explanations may include recruitment of patients who may be less capable of good adherence because of co-morbid illness or motivation. Our analysis of baseline features provides no clear evidence for this, although participants from LIONs were more likely to report a prior myocardial infarction and to have a lower score on the Modified Mini Mental State Examination. Alternatively, research staff at LION coordinating center may have spent less effort on supporting participants for good adherence in a trade off with effort spent on recruitment. Our findings indicate that investigators who use the LION strategy must assure that support for individual participants is preserved as larger numbers of participants are enrolled.

The LION strategy was more expensive than the fee-for-service strategy at other sites participating in the IRIS trial. Within our study design, we were not able to determine the reasons for the discrepancy. However, we believe there are opportunities to lower costs within the LION system. First, require strong evidence of network size or participant availability prior to engaging a LION. This requirement might assure that a LION could produce the number of enrollments required to achieve a target per-patient cost. A LION that cannot achieve a pre-specified network size might still be funded, but at an adjusted rate. Second, reduce the interval from initiation to peak performance. We believe this can be accomplished by improved training of researchers to prepare them for the LION system. If the LION strategy becomes common, furthermore, IRBs and hospitals may become more efficient in accommodating LION requirements. Third, use remote access to electronic records to more efficiently confirm participant eligibility. Fourth, monitor costs per-participant in real time for a disciplined approach to fiscal management. Sites that exceed a specific cost, compared with the fee-for-service strategy, could be immediately switched back to the fee-for-service strategy. Despite the higher per-patient cost at LION sites, it is possible the LION strategy will reduce overall research costs by shortening the duration of the research.

Our results validate the LION approach and establish its effectiveness for enhancing clinical trial research. Key features of this approach include central coordination of research at regional hospitals and travelling coordinators who use active surveillance and patient outreach to find and engage participants in research. This approach could be used for clinical trials in many disease areas, but will benefit from further development. Refinements in administration, researcher training, performance monitoring, and accounting practices may result in enhanced cost effectiveness. With these refinements, LIONs could be constructed to support multiple studies simultaneously and in sequence over many years.

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Acknowledgments		
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Glossary

AIDS	Acquired Immunodeficiency Syndrome
BMI	Body Mass Index (kg/m^2)
CRC	Canadian Stroke Consortium
CGP	Cooperative Group Program (of the National Cancer Institute)
FTE	Full Time Equivalent
HIPAA	The Health Insurance Portability and Accountability Act
HOMA	Homeostasis Model Assessment of Insulin Resistance
IRB	Institutional Review Board
IRIS	Insulin Resistance after Stroke Trial
LION	Local Identification and Outreach Network
MI	Myocardial infarction
MMSE	Modified Mini Mental State Examination
NCI	National Cancer Institute
NETT	Neurological Emergency Treatment Trials Network
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
RCT	Randomized Controlled Trial
TIA	Transient Ischemic Attack
UKCRN	United Kingdom Clinical Research Network

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Table 1

Characteristics of Local Identification and Outreach Networks Participating in the Validation Study*

	# of Institutions in Network					Staff	
Network	**Hospitals**	**Practices**	**Total # Hospital Beds In Network**	**Radius (miles)†**	**Average # Age Eligible Patients with Ischemic Stroke/TIA Identified each Month**	**# FTE Neurologists**	**# FTE Coordinators**
1	8	1	2029	50	35	0.20	1
2	6	0	2429	25	155	0.20	2
3	5	1	2532	15	117	0.20	2
4	5	3	1945	45	77	0.20	1
5	2	4	750	5	27	0.20	2
Total (mean)	26 (5.2)	9 (1.8)	9685 (1937)	(28)	411 (82)		

*as of 6/30/09

†Distance from coordinating center to most distal hospital or practice in the LION.

Table 2

Recruitment Performance of LION sites before and after implementation of LIONs[*].

	Pre-LION Interval				LION Interval			
	Blood Screen		Randomized		Blood Screen		Randomized	
Member Institution	Total	Average/Mo	Total	Average/Mo	Total	Average/Mo	Total	Average/Mo
1	26	0.8	14	0.4	37	1.7	16	0.7
2	39	1.6	19	0.8	82	3.4	37	1.5
3	37	1.3	21	0.7	94	3.9	34	1.4
4	25	1.0	12	0.5	59	2.7	27	1.2
5	58	2.2	31	1.2	141	5.9	65	2.7
Total/Mean	185	1.4	97	0.7	413	3.5	179	1.5
Total/Mean for Non-LION Sites[†]	924	0.8	517	0.5	1533	0.8	715	0.4

[*]For member institution 2, 3, and 5, and all non-LION sites, the pre-LION interval was 1/1/05 to 6/30/07. For member institutions 1 and 4, the pre-LION interval was 1/1/05 to 8/31/07. Sites were activated to begin blood screening at various intervals after 1/1/05. For all sites, the LION interval ended 6/30/09.

[†]N= 86 sites that enrolled at least one IRIS participant for a screening blood test during 7/1/07-6/30/09, excluding original LION site in Connecticut.

Table 3

Baseline Characteristics of Participants Randomized from LIONs Compared with Other Sites during 7/1/07 to 6/30/09.

	Research Site*		
Characteristic†	**LION (n=179)**	**Non-LION (n=715)**	**P**
Age, years (mean)	62 +10	62 +11	.75
Female Gender, %	35%	38%	.53
Years of schooling	13	13	.96
Hispanic Ethnicity	1%	3%	.17
Black Race	12%	12%	.79
History of Myocardial Infarction	11%	5%	.01
Modified MMSE Score‡	92	94	.02
BMI, kg/m^2	30 +5	31 +6	.29
HOMA	5.3 +2.2	5.1 +2.4	.27
Stroke, %	84%	84%	.96
NIH Stroke Scale Score, mean	1.1 +1.9	1.0 +1.9	.50
Modified Rankin Grade			
No symptoms at all	46%	45%	.52
No significant disability	28%	31%	
Slight disability	15%	16%	
Moderate disability	6%	6%	
Moderately severe disability	4%	2%	
Severe disability	0%	0%	

*The Connecticut LION is excluded from this table. The non-LION sites are the 86 sites that enrolled at least one IRIS participant for a screening blood test during 7/1/07-6/30/09.

†Missing data: Ethnicity: 1 in non-LIONs; Black race: 3 in non-LIONs

‡MMSE=Modified Mini-Mental State Examination

Table 4

Selected Indicators of Quality*

	LION Sites			All Other Sites†		
	Due	Randomized, Completed or Returned		Due	Randomized, Completed or Returned	
	N	N	%	N	N	%
Screened-eligible patients randomized‡	225	185	82%	820	716	87%
Quarterly Telephone Follow-ups	1211	1121	93%	5168	5006	97%
Annual Interviews	54	51	94%	298	278	93%
Annual Phlebotomies	54	50	93%	298	280	94%
Pill Bottles returned	385	333	86%	1759	1593	91%
Time from event to randomization, mean	86 days			90 days		
Participants with good adherence§	80/153 (52%)			418/629 (66%)		
Participants retained in cohort¶	172/179 (96%)			682/715 (95%)		
Queries per randomized participant**	1557/179 = 8.7			6750/715 = 9.4		

*Data are for participants screened with blood tests or randomized during period 7/1/07 (9/1/07 for member institutions 1 and 4) through 6/30/09. Follow-up refers to contacts and phlebotomies due through 6/30/2009. Pill bottles refer to bottles dispensed to the randomized cohort through 6/30/09, although they may be due back/returned after the interval. Queries were generated during the interval above but could have been resolved subsequently.

†Excluding the Connecticut LION which was the development LION.

‡Screened-eligible refers to participants who were eligible for randomization after the screening blood test based on with HOMA>3.0, no diabetes, and no other exclusion factor. Calculation of % randomized includes patients screened during LION interval but randomized after 6/30/09.

§Good adherence to the study drug = taking ≥ 80% of study pills prescribed.

¶Participants not lost-to-follow up as a result of a request to be removed from the study or inability to be located after one year of attempt by the study team.

**Queries are most commonly generated for missing, incomplete, or out-of-range data.

Table 5

A taxonomy of network models for recruitment in randomized clinical trials.

Type	Description	Network Infrastructure is Sponsored Independent of Any Trial	Typical Geographic Distribution	Purpose	Traveling Coordinators	Examples*
Convenience	A sponsor contracts with investigators at multiple hospitals, practices, or other institutions to identify, enroll, and follow participants. Each investigator must assemble an institutional research team, including coordinators.	No	Unlimited	Single Trial	No	Most Trials
Gateway	These networks are comprised of investigators who are typically working in the same specialty. Sponsors apply to the network administration for approval of the protocol and permission to approach members who have expressed interest in the study.	Yes	National	Multiple Trials	No	CSC, UKCRN
Fully Managed Disease Community	One clinical coordinating center and data center support multiple trials, concurrently and over time, in one disease area using pre-approved centers (i.e., hospitals or practices). Trial protocols may be developed internally or through external peer review.	Yes	Regional or National	Multiple Trials	No	CGP of NCI, NETT, AIDS Clinical trials Cooperative Groups
Corporate	Coordinating and data centers maintained by health maintenance organizations support trials at their facilities. Trials may be developed internally or externally.	Yes	Regional	Multiple Trials	No	Kaiser Permanente
Outreach	One regional coordinating center sends coordinators to collaborating regional hospitals to complete participant recruitment and follow-up. This model may includes active surveillance for potential participants and home visits to reduce barriers to trial participation.	No	Regional	Single Trial	Yes	LION

*CSC=Canadian Stroke Consortium, UKCRN=United Kingdom Clinical Research Network, CGP of NCI=Cooperative Group Program of the National Cancer Institute, NETT=Neurological Emergency Treatment Trials Network of the National Institutes of Neurological Disorders and Stroke, LION=Local identification and Outreach Networks.