Clinical Trials – And Why They Are Important

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From Bench to Bedside ONLY happens with Clinical Trials

- Almost all the medicines you take today, from medications for your blood pressure to the chemotherapy you may be taking, are available to you only because patients like yourselves participated in the various stages of clinical trial development.

- Thanks to the IWMF, LLS and researchers in academic labs and in the pharmaceutical industry, we are making dramatic progress in developing newer, more effective and less toxic agents to treat blood cancers including WM.

- Without increasing clinical trial participation, we will never be able to take advantage of the dramatic new biological insights and improve our therapies.

Some Clinical Trial Stats….

- *¼ of trials sites don't accrue at all*
- *another ¼ of trials don't finish*
- *only ~3% of cancer patients ever participate in a clinical trial*

Clinical trials are expensive and raise the cost of care if they don't answer important questions.

Making trials more efficient and more feasible for patients is a critical focus for LLS

- To advance our science
- To reduce the cost of care for all patients

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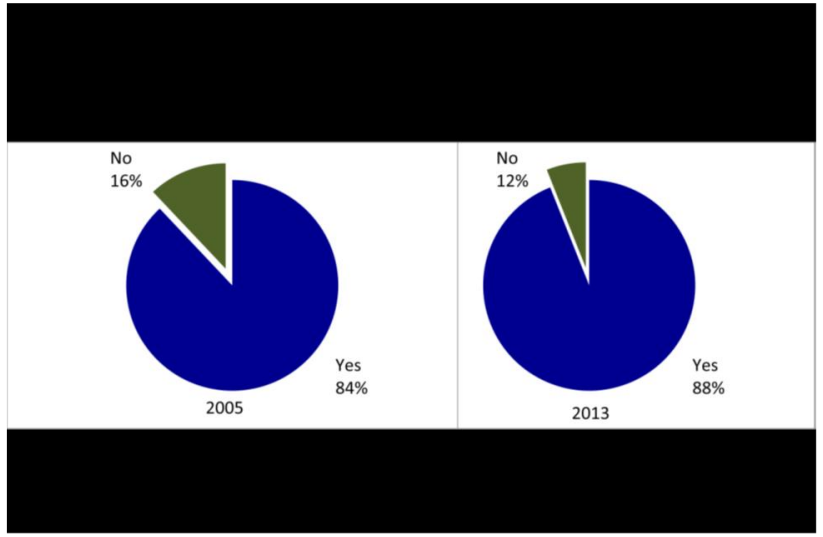
Changing the Conversation about Clinical Trials

- Patient Barriers
  - Fear of being a “guinea pig”
  - Misunderstanding the role of placebos in oncology
  - Lack of awareness of opportunities
  - Complexity of access and entry criteria stringency

- Physician Barriers
  - Lack of awareness of opportunities
  - Insufficient time to research trials for all diseases
  - Disincentive of “losing” patient to another center

The Majority of Volunteers Would Participate in a Clinical Trial Again



Source: CISCPR-Center for Information and Study on Clinical Research Participation, 2013

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HOW DOES A DRUG GET DEVELOPED?

- Laboratory research (academic or pharmaceutical)
  - targeting a particular molecular pathway, immunologic pathway or disease process
- Activity discovered against cancer *in vitro* (in the test tube)
  - compounds are screened or
  - molecules (antibodies, vectors) are synthesized
- Models explored (in an academic lab or company)

It may take years to understand the mechanism of action in cell lines and in animal tumors before a particular discovery can be turned into a drug.

NEXT STEPS

- A laboratory compound suitable for cells (or even animals) is rarely suitable for humans
  - Chemistry and formulation work
    - Optimized absorption in the human gut, adequate concentrations for activity
    - Purity and quantity required for human testing
- Toxicology testing
  - Safety studies (depending on the type of agent) in animal models required to allow studies in humans
- An Investigational New Drug (IND) application is submitted to the health authorities
  - extensive documentation of how the drug will be produced and stored
  - clinical plans for development
  - how patient safety will be assured

Phase 1 - "Entry-Into-Human" trial

- Phase 1 is usually the first time any human has received the drug
- Critical findings for Phase 1:
  - Pharmacology : how much drug to give, how it is metabolized and excreted, and how it should be dosed (both amount and frequency)
  - Dosing in step-wise increments to learn about harmful side effects, as well as beneficial effects.
    - Goal is always to err on the side of safety
    - Start at doses well below side effects in animals
    - Dose testing in Phase 1 continues either to a maximum biological dose (where an effect is predicted to be seen) or to a maximum tolerated dose

Patients must agree to the testing required by signing an informed consent. The amount of testing, days at the clinic, requirements for biopsies and scans may be extensive to determine the best way to give the drug in the future.

Phase 2 trials

- Phase 2 trials often involve more patients.
- Analysis for drug's efficacy and safety in patients selected by disease characteristics
- May be in combination with or in comparison to a standard of care treatment.
  - Specific eligibility criteria for selecting patients.
    - particular stages of a given disease
    - the number of prior treatments,
    - general health characteristics,
    - tumor biopsy, or pathologic characteristics

  This may be frustrating for patients who don't fit the entry criteria
- The restricted population, number of patients and the testing performed are based on statistical evidence to support benefits superior to available treatments

Phase 3 Trials

- Chiefly designed to statistically demonstrate clinical benefit versus a standard treatment.
  - Phase 3 trials involve more patients and an increased number of locations.
  - Most Phase 3 trials are done to seek approval for marketing.
  - Phase 3 trials are generally randomized and are often double-blinded.
    - **Randomization** patients are assigned to a particular treatment by chance (may or may not contain the new drug).
    - **Double-blinded** neither the patient nor the treating physician knows which treatment the patient is getting.
    - Placebos ALONE are rarely ever used in oncology trials, standard of care drug(s) may be given (what you'd get if you weren't on a trial. T
    - Placebos may be given with SOC as a "look alike" to maintain 'blinding'.
- Results of Phase 3 studies are presented to health authorities as part of a new drug application (NDA).

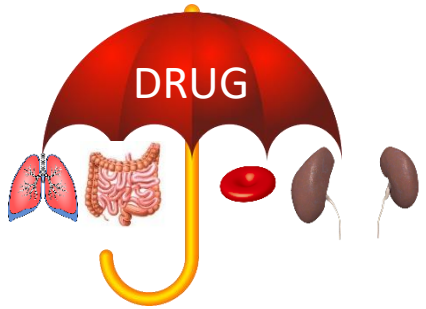
WHY DO TRIALS TAKE SO LONG?

- Early phases may be stop and go – change the characteristics of the drug, change dosing, change safety criteria.
- Lack of an adequate signal – or the wrong test population. The majority of new agents still fail in clinical testing.
- Phase 3 trials often take years to perform.
  - large number of patients to demonstrate statistical improvement over standard treatment
  - endpoints in oncology are frequently progression free survival or overall survival
    - median overall survival for many diseases is longer than in the past
      - Tumor shrinkage alone may not predict survival
    - safeguards to protect participants mean more patients and more time
      - Delicate balance between getting new medicines to patients, and discovering rare (1/1,000 or 1 /100,000) but important side effects.
      - Companies often agree to post-marketing or Phase 4 evaluations to learn about these rare but important side effects.

What is being done to speed up clinical trials?

- New types/phases designs
  - Phase 1/2 or Phase 2/3 designs, Multi-arm/drop-add arm trials, trials targeting a pathway rather than a disease or a disease with multiple agents

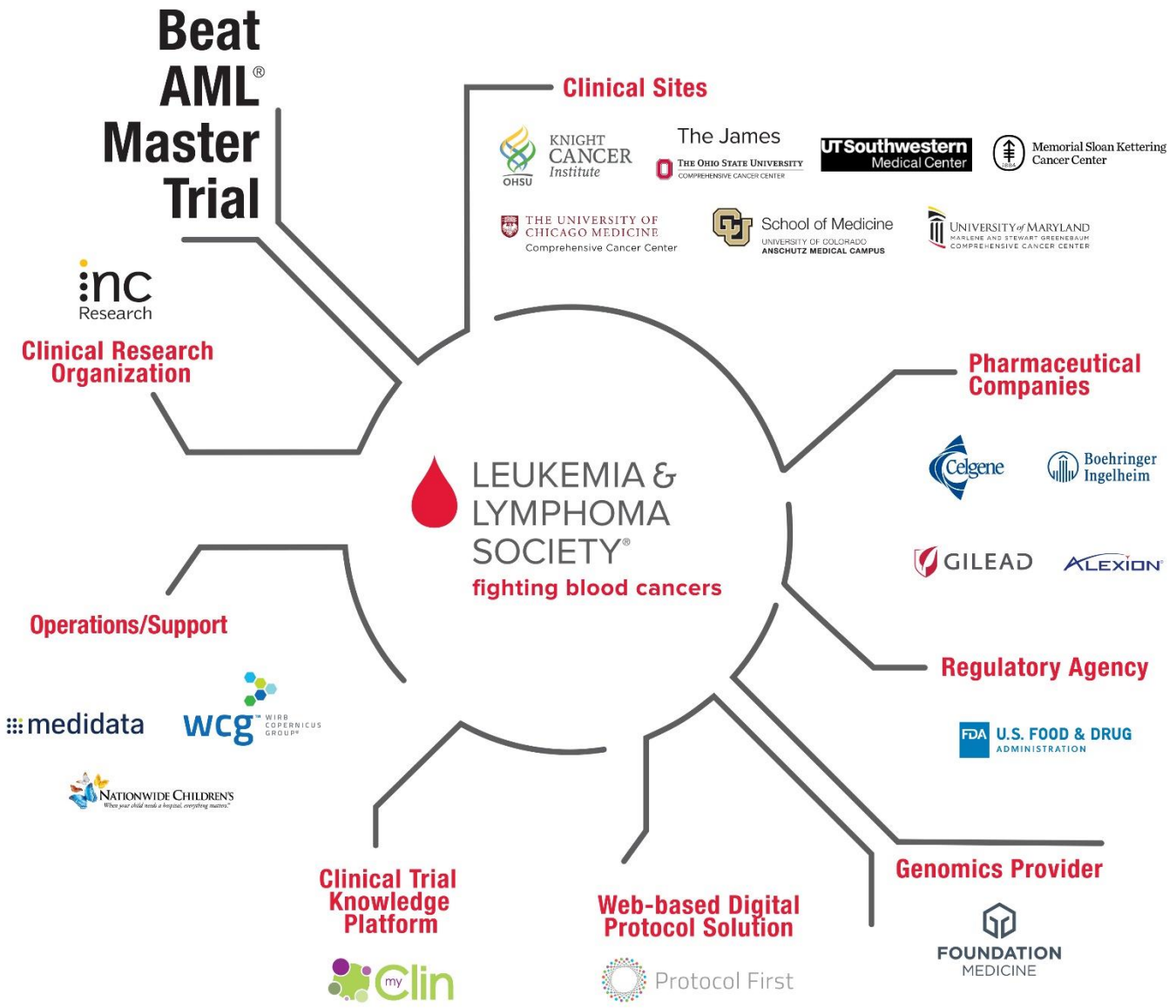
BASKET



UMBRELLA

- New regulations for approval breakthrough
  - FDA Breakthrough Therapy Designation
    - expedite development of drugs for serious or life-threatening conditions
  - Accelerated approval
    - intended for drugs that effect a “surrogate endpoint” reasonably likely to predict benefit on survival
  - Priority review
    - FDA agrees to complete review and act on an application within 6 months rather than the standard 10 months.

BEAT AML



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Master Trials like BEAT AML may lead to more efficient development timelines

- "Neutral parties" holding the IND means:
  - Multiple partners more easily collaborate in the same trial
  - Fewer contract and site/specific negotiations
- Multiple arms vs. one drug at a time ----- every patient who gets tested has a clinical trial option
- Flexible arms and protocol design allow:
  - Switching agents and combinations in and out of the trial without designing a new trial
  - The trial to continues while a new arm is being reviewed
- Open to novel-novel combinations
  - We now have different pharma partners working together on the same arm of a trial

What we need to do

- More patients and their doctors need to consider clinical trials --- and not just as a “last resort” but as a way to move science forward for yourself and for future patients.

- We, as clinical trial physicians need to think about more efficient, novel and rapid clinical trial designs which allow more patients to get benefit and with less “uprooting” in order to participate.

- We, as advocacy organizations need to think about what patients need to make participation feasible; help in navigating clinical trial options, help in navigating insurance coverage for trials, and assistance in personal support (travel, information, financial support etc.)

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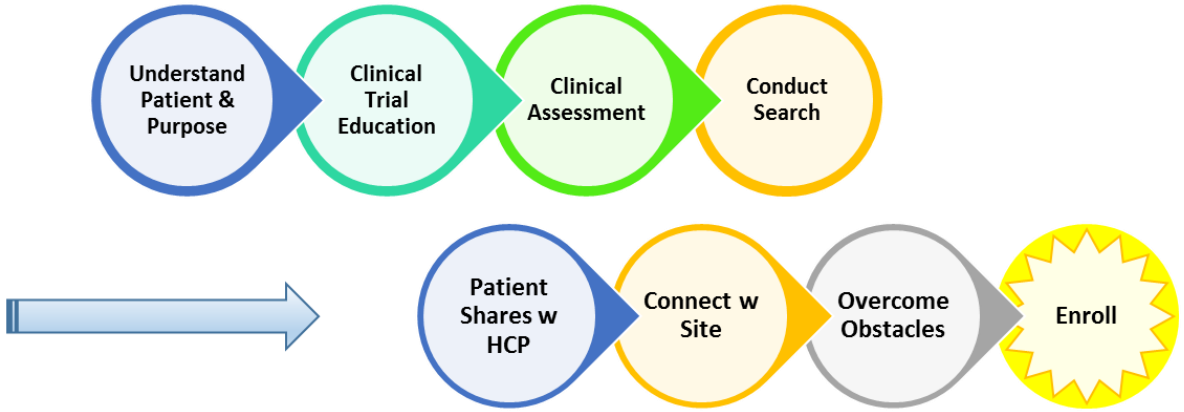
The LLS Clinical Trials Service Center (CTSC)

- Highly trained nurses provide personalized 1:1 navigation and education
- Detailed health information and entry criteria assessed
  - What the patient wants from clinical trial participation
  - What support the patient has; ability to travel, caregiver, personal responsibilities
  - Focus on access: Insurance, travel feasibility and other factors that discourage participation
- Contact sites to be certain trial is open and accruing BEFORE patient contacts site
- Provide patient with a curated professional, detailed, *individualized* search to discuss with their HCP



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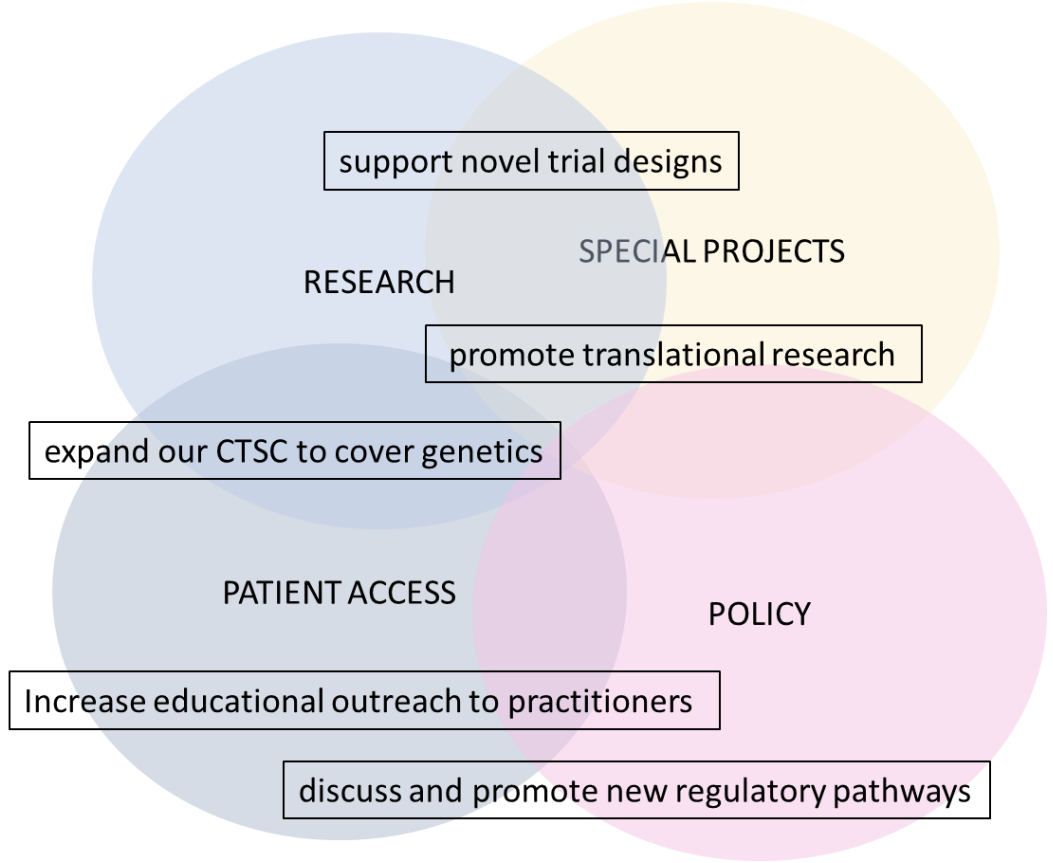
LLS Multi-armed Approach to Impact Clinical Trials

- Expand our industry-leading clinical trial navigation service
- Educate patients and practitioners about the importance and benefits of trial participation
- Increase our impact by providing cancer genetic counseling
- Advocate for new approval pathways
- Improve the speed, access and benefit for patients of clinical trials (master trials, novel trial designs)



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Registries as a “Real World” Clinical Trial

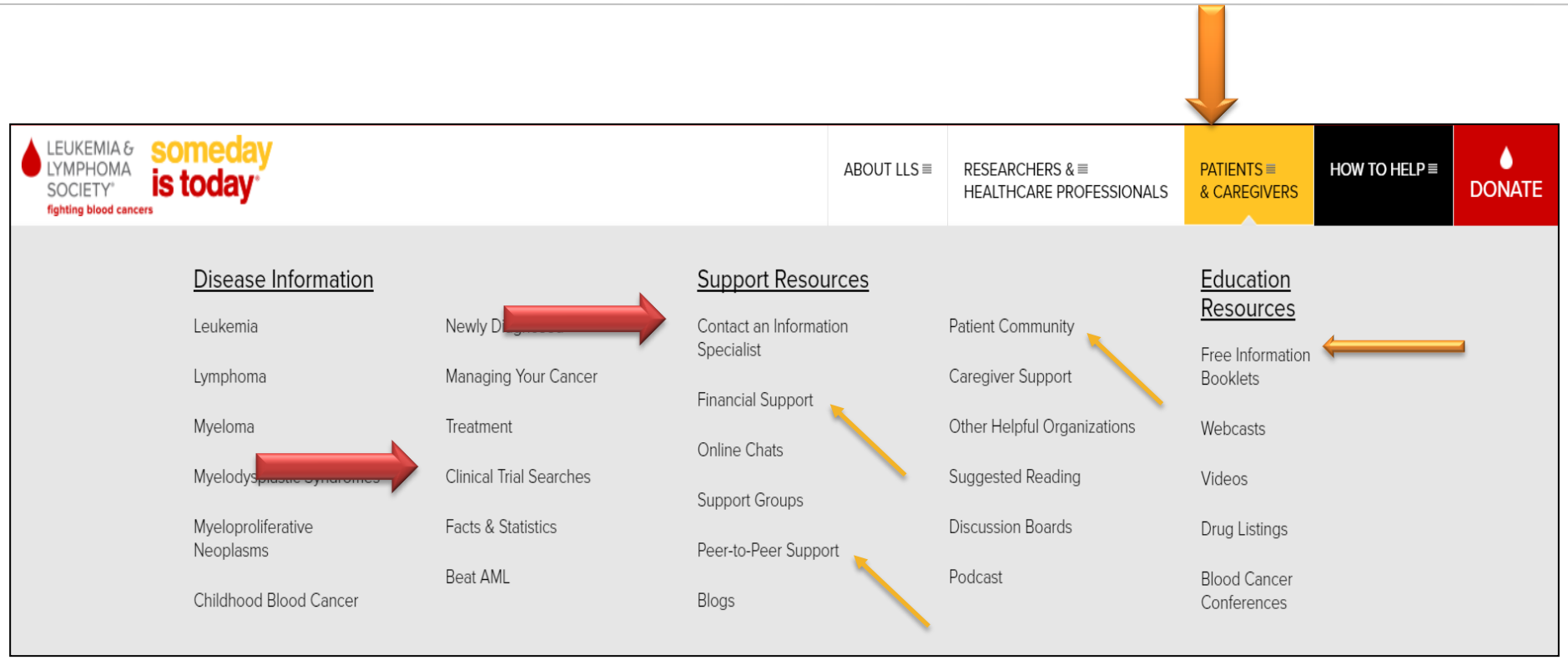
LLS Patient Registry

Where patients consent to provide their Electronic Health Records

GOAL:

- All medical records are de-identified and combined into one database
- LLS allows researchers to examine these de-identified records and publish research results using this data for improving care
- Answers of importance to patients can be queried within the database
- Identify patterns
  - of improved outcomes
  - of untoward side effects
- “Real world” data on treatment results can create a **Virtual Control Arm** decreasing the number of subjects needed for control arms on clinical trials

LLS Website – One-stop Shopping for Resources/Support



OR CALL OUR INFORMATION RESOURCE SPECIALISTS: 1 (800) 955-4572

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