The Clinical Trials Process

an educated patient's guide

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DISCLAIMER

- I am an employee of Hoffmann-LaRoche, and will not mention any off-label use of agents.

Do Clinical Trials Work?

- 2013 Sunday New York Times review raised this question because:
  - Trials take too long to achieve results
  - Trials cost too much
  - Trials don't always show measurable benefit

Questioned the Pharma industry's willingness to take risk

Questioned if the regulators are too conservative

Both Pharma and patients can agree

- Newly developed, more effective medicines need to get to the right patients, faster and less expensively.
- A balance of patient safety and speed must be brokered

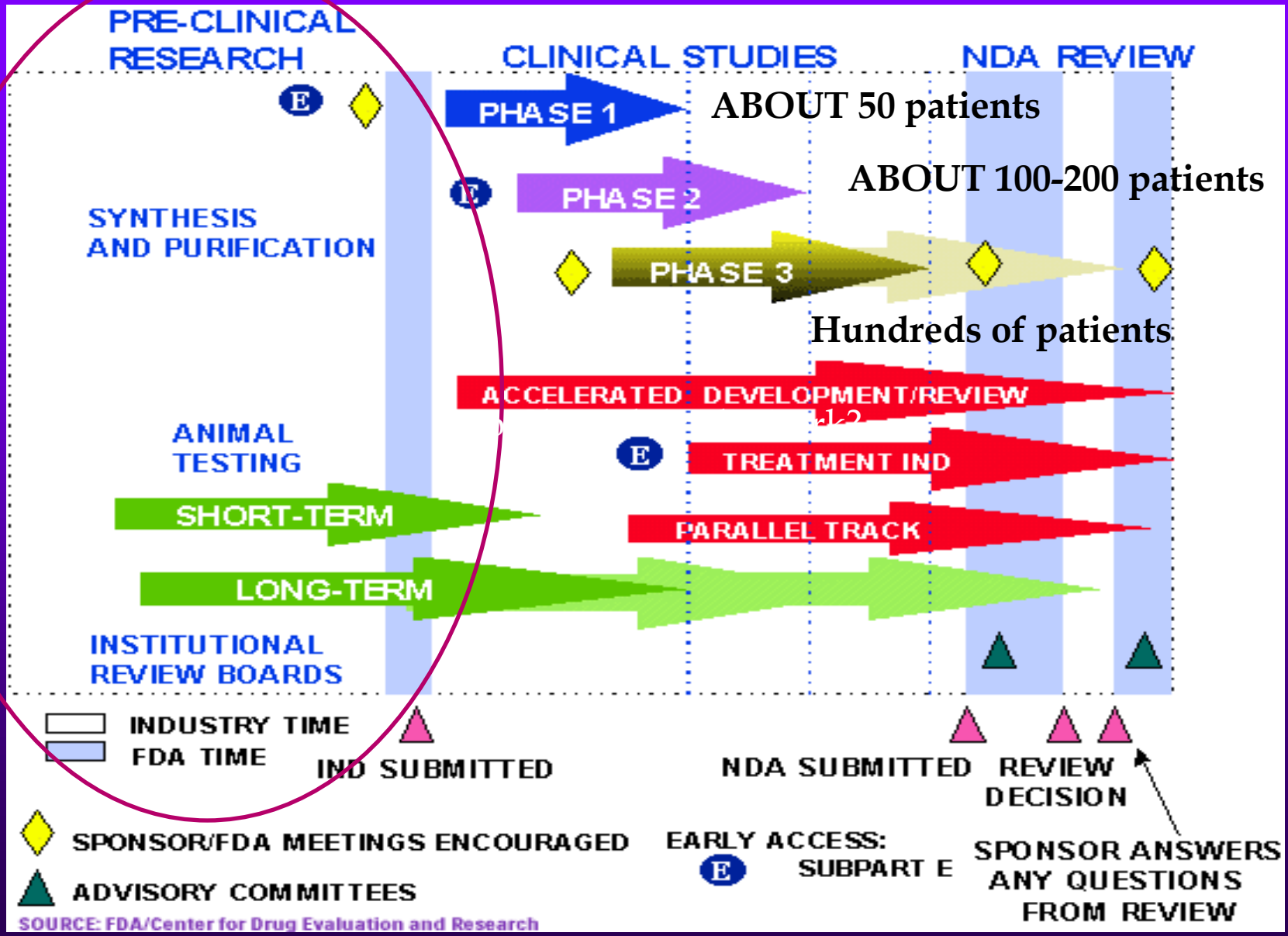
Be an Educated Consumer

- It is not always clear what the purpose of a given trial may be, what a participant should expect, and who really stands to benefit from the patient's participation.
- While there are no "one-size fits all" answers to the question "Should you participate?", a clear understanding of the questions and complexities involved can help you obtain the necessary information to make an informed decision.
- Informed Consent forms are legal documents and do not necessarily provide the information in a logical and digestible fashion.

What We Will Cover:

- THE DRUG DEVELOPMENT PROCESS
  - Some basics
- CLINICAL TRIALS – the 5 "Ws"
  - More basics
- CLINICAL TRIAL "LINGO" -
  - **How to read a clinical trial description**
- WHY DOES DRUG DEVELOPMENT TAKE SO LONG?
  - And what are we doing about it?
- QUESTIONS TO ASK ABOUT TRIAL PARTICIPATION
  - **What to ask your doctor**
  - **What to ask yourself**

Drug Development Process



How does a new drug get developed?

- **Discovery**
- Optimization
- ADME" stands for absorption, distribution, metabolism and excretion
- Toxicology
- PK,PD Modeling

How does a drug target get discovered?

- Scientist looks through a panel of compounds for activity
- Scientist believes there is a particular target or pathway which is relevant for cancer and designs a drug for that pathway
- Serendipity

Lots of science…….

- Many *in vitro* studies are performed to show that the target is "druggable" and that it looks efficacious against models of human cancer.
- Animal models for cancer efficacy showing that the target is a valid one

How does a new drug get developed?

- Discovery
- **Optimization**
- **"ADME" stands for absorption, distribution, metabolism and excretion**
- Toxicology
- PK,PD Modeling

Drug Development 101

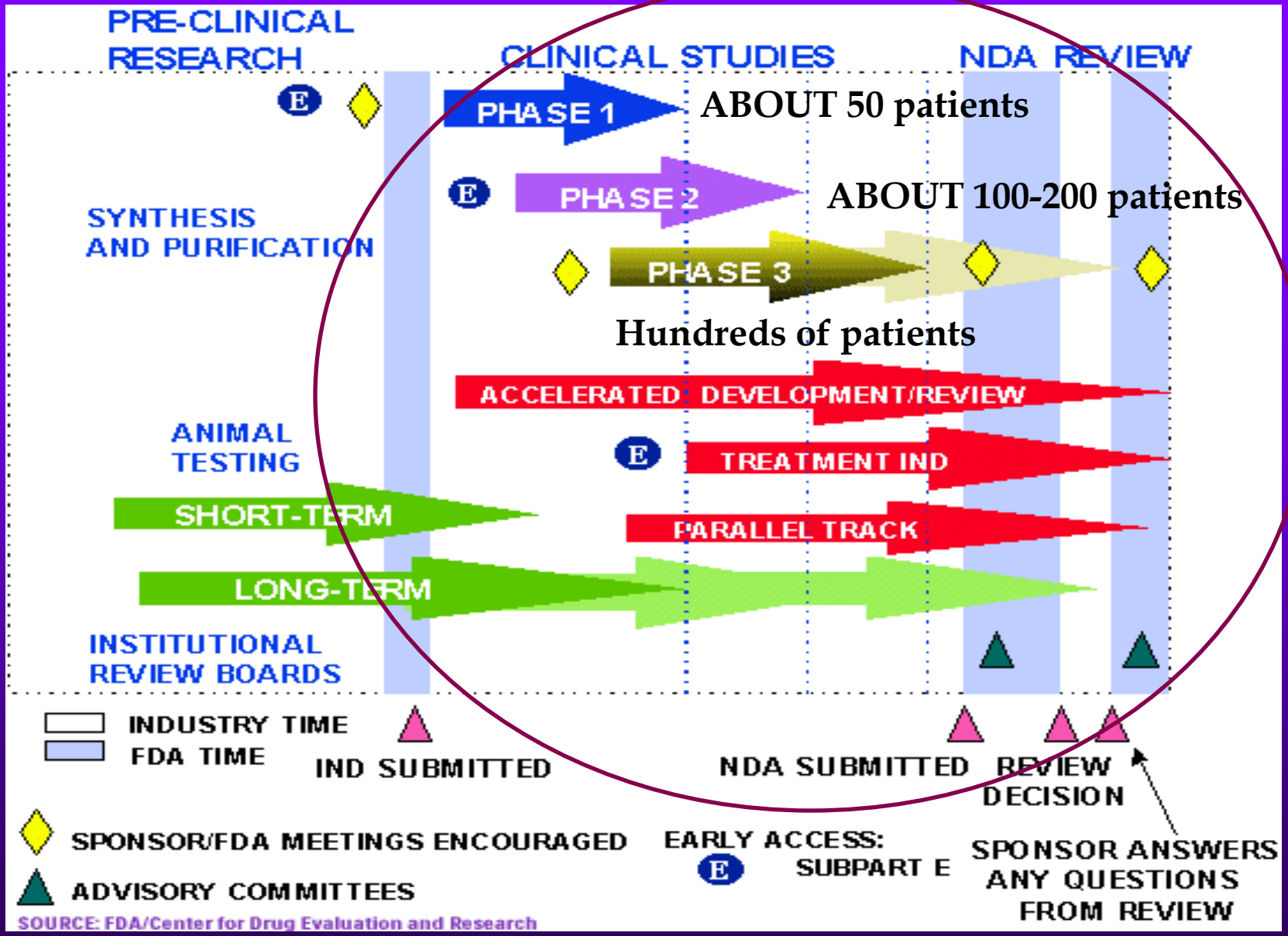
- Optimization: Once a target has been identified and a chemist has attempted to synthesize the compound, further specific laboratory testing (chemistry, and formulation development) is performed to see if the compound can be made into a form suitable for administering to humans
  - Synthesis, stability, solubility
- ADME: Testing the compound's properties in animals and other model systems to see how it is absorbed, distributed, metabolized and excreted

How does a new drug get developed?

- Discovery
- Optimization
- "ADME" stands for absorption, distribution, metabolism and excretion
- **Toxicology**
- **PK,PD Modeling**

Toxicology and Modeling for Human Dosing

- Specific studies in animals are performed to determine a dose level which is non-toxic
- These studies are specified by health authorities and must be conducted in a specific fashion prior to proposing human testing
- This dose level is then adapted to what might be expected in a human by modeling toxicity, metabolism and excretion from animal data


PRE-CLINICAL RESEARCH
CLINICAL STUDIES
NDA REVIEW
E
PHASE 1
ABOUT 50 patients
E
PHASE 2
ABOUT 100-200 patients
SYNTHESIS AND PURIFICATION
PHASE 3
Hundreds of patients
ACCELERATED DEVELOPMENT/REVIEW
ANIMAL TESTING
E
TREATMENT IND
SHORT-TERM
PARALLEL TRACK
LONG-TERM
INSTITUTIONAL REVIEW BOARDS
INDUSTRY TIME
FDA TIME
IND SUBMITTED
NDA SUBMITTED
REVIEW DECISION
SPONSOR/FDA MEETINGS ENCOURAGED
EARLY ACCESS:
E
SUBPART E
SPONSOR ANSWERS ANY QUESTIONS FROM REVIEW
ADVISORY COMMITTEES
SOURCE: FDA/Center for Drug Evaluation and Research

Drug Development 101

- IND (investigational new drug) application submitted to the FDA and to European Health Authorities
- Protocol, Investigator's Brochure, Preclinical and Toxicology reports are reviewed
- With approval, the protocol is then submitted to hospital institutional review boards and ethics committees
- Start the Phase 1 clinical trial "Entry into Human" (EIH) or 1st in human.

Clinical Trials – 5 W's

- **WHO** – defined criteria based on stage of disease, prior treatments, other illnesses – not always the "average" patient
- **WHAT** – A specific scientific experiment with set criteria for entry, treatment and follow up. May be sponsored by investigator, pharmaceutical company, cooperative group
- **WHEN** – may be for initial treatment, relapse, observation/prevention
- **WHERE** – usually at large medical centers although increasingly available through cooperative groups at a more local level. Only specific investigators are able to participate
- **WHY** – To develop new medicines. Possible to get access to new treatments - - possible to help understanding of the disease for others in the future

Helpful Clinical Trial "Lingo"

- Clinical Trial Phases;
  - **Phase 0 – preclinical testing and toxicology**
  - **Phase 1 – First in human trials for safety, pharmacology, mechanism**
  - **Phase 2 – Efficacy (possibly in specific diseases)**
  - **Phase 3 – Randomization against "standard of care" to prove is better**
  - **Phase 4 – Post-marketing studies**
  - **Others - pharmacology, new formulations of a drug, different dosing and schedules, or testing of biomarkers which predict activity,**
- Design Elements
  - Blinded vs. Open-label
  - Controlled (placebo vs. other comparison)
  - Randomized
- Endpoints
  - Overall Survival (OS, mOS)
  - Progression-Free Survival (PFS)
  - Time to Progression (TTP)
  - Overall Response Rate (ORR)
    - Complete Remission (CR - does not mean cure)
    - Partial Remission (PR)
    - Minor Response (MR)
    - Stable Disease (SD)
    - Progressive Disease (PD)

Phase 1 Trials

- Phase 1 (in Oncology) is generally "Entry-Into-Human" - the first time any human receives the drug.
  - understand the pharmacology of the new agent;
  - how much drug to give, how it is metabolized, and how it should be dosed (both dosage amount and frequency)
- Accomplished with step-wise increments in dose to learn about harmful side-effects, as well as beneficial effects.
  - In Phase 1 the goal is always to err on the side of safety, so the dose given to initial study patients may not be the effective or final dose.
- Phase 1 studies start at doses well below the doses where side effects were seen in animals,
  - Continue either to a maximum biological dose (where an effect is predicted to be seen), or to a maximum tolerated dose.
  - Increasingly Ph1 studies analyze effects of the drug in blood or tissues. Patients participating must agree to the testing required for the study by signing an informed consent.
  - May have extensive testing, number of days at the clinic, and requirements for biopsies and scans

Phase 2 Trials

- Phase 2 trials generally involve more patients
  - Analyze the drug's efficacy and safety in selected patients chosen by disease characteristics.
  - Contain more specific eligibility criteria for selecting patients.
    - e.g.: stage of disease, number of prior treatments, general health, tumor biopsy or pathologic characteristics.
    - The number of patients in Ph2 and the requirements are based on the level of statistical assurance needed to support clinical benefit.
  - May be performed in combination with or comparison to a standard of care treatment.

- In order to participate in a Phase 2 trial, patients need to meet all the entry criteria to ensure that the study data is reliable. This can be frustrating, particularly if one's disease characteristics differ from the norm.
- For researchers a valid concern is that, highly selected populations may not adequately reflect the more general population of patients with a given condition.
- Ph2 is done with an eye to predicting what will happen in a larger population of patients in Ph3 against the best treatment available.

Phase 3 Trials

- Phase 3 trials, based on Phase 2 data, are designed to statistically demonstrate clinical benefit versus a standard treatment.
  - Phase 3 trials involve more patients, and an increased number of locations.
    - May take years to perform
    - Are usually the most expensive part of the development process
    - Done to seek approval for marketing.
  - Phase 3 trials are generally randomized, and are often double-blinded.
    - Randomization means that patients are assigned to a particular treatment by chance (the test treatment may or may not contain the new drug being tested). Neither patient nor doctor can choose.
    - Double-blinded means that neither the patient, nor the treating physicians know which treatment the patient is getting.
    - Placebos are rare in oncology trials, but participants in a Phase 3 trial, one may get a standard of care drug that is also available for those not participating in the trial.
- Results of Phase 3 studies are presented to health authorities as part of a new drug application (NDA).

Why does drug development take so long?

- Endpoints required for marketing authorization (e.g. overall survival) may take years *discussed on next slide
- Not from lack of spending
  - R&D spending from the 12 leading pharmaceutical companies over a 5 year period was estimated at >800 billion to gain approval for just 139 drugs (Avik Roy, Manhattan Institute 2012)
- High cost of R&D leads to higher drug costs
  - Hurts patient access
  - Drives up insurance rates
  - Incents companies to go for "big indications" with high potential return rather than just following the science
- Lots of money is spent on failure

What can we do to increase the successes?

Look at Study Endpoints
Effects on study length and outcome

- Usual Ph3 endpoints in Oncology are PFS (progression free survival) and/or OS (overall survival)
- With improvements in treatment, median overall survival for many diseases is longer than in the past
  - We may have to wait years to see benefit based on survival which slow development
  - We need valid "surrogate" endpoints to predict what will happen years later
- Researchers and regulators are carefully examining these questions
- It may seem obvious that tumor shrinking would predict improvement in progression free survival; but this is not always the case.
  - For instance, a toxicity may offset any improvement in OS
- Each particular disease must be examined for adequate markers of efficacy that can serve as reliable "surrogates" for helping patients live longer.

Example: why traditional trial designs aren't optimal for WM

Table 2. — Feasibility of Conducting RCTs in Rare Diseases: Sample Size Calculations

Disease	Baseline Survival on the Current-Standard Treatments	Hypothesized (expected) Improvement on a New Treatment (realistic scenario, decrease in relative risk of death by 20%; hazard ratio = 0.8) (sample size) (assumed 3-yr accrual + 2-yr follow-up; 10% lost to follow-up)	Hypothesized (expected) Improvement on a New Treatment (overoptimistic scenario, decrease in relative risk of death by 50%; hazard ratio = 0.5) (sample size) (assumed 3-yr accrual + 2-yr follow-up; 10% lost to follow-up)	Prevalence (total number of patients available in the United States)
Indolent T-cell LGL leukemia	Median survival >10 yrs	3,380	439	160 patients/yr
Anaplastic large T-cell non-Hodgkin's lymphoma (ALCL)	80% (5 year survival, ALK+)	5,050	662	1,800 patients/yr
Peripheral T-cell lymphoma, unspecified	25% (5-yr survival)	1,143	140	4,000 patients/yr

From Behera *et al* Cancer Control 2007

For WM in the US there are about 1400 new patients/year

Perform smarter trials and fail earlier

Failure of a compound in Phase 3 is a huge time, money and most importantly patient "expense"

- More early science
  - Laboratory and early clinical evaluation are much less expensive than an international Phase 3 trial
- More biomarkers
  - This means more blood, more biopsies and more scans
- More "Proof of Mechanism" trials
  - Trying to prove the drug's mechanism of action before looking for clinical results (does the drug work the way you predicted it would? (yes/no))
- More "rational" combination trials earlier.
  - The use of fewer cytotoxics (traditional chemotherapies) – means more targeted agents and more need for combinations in order to see benefits.
- More novel trial designs
  - Allowing flexibility to change design as trial progresses
  - 2 NME designs - Need to cooperate with other pharmaceutical/biotech companies earlier in development

The WM Patient's View of the World

Waldenström's

What to Ask your Doctor about a trial

- What is the scientific rationale for use of this agent in WM?
- What is the phase of the study and what is the goal or endpoint?
- Has it been used in humans before, and if so, what are the expected side-effects?
- How is the treatment given and for how long?
- How many follow-up appointments, blood tests, scans and other assessments will I need to make?
- How many tests are specific to the study versus being done as part of normal care?
- What is the likelihood that I will be helped by participation?
- Are there approved or standard therapies which make sense to use first?

What to Ask Yourself about trial participation

- Am I willing to have biopsies or other studies (x-rays, blood work) required for participation?
- Am I ready to participate in order to help others in the future if this has only a small chance to work for me?
- Am I a person who believes in the scientific process?
- Am I willing to follow all of the elements of the research study, even if they are inconvenient? Do I have adequate help/support?

PLUG FOR THE IWMF

- Advocate for and help fund research and clinical trials which will get WM patients access to the latest advances
- Your participation in the IWMF allows WM Researchers to approach the Pharma industry with a promise of patients with defined characteristics and numbers to speed development

While it is not always possible or necessary…….

IF YOU CAN…..

PARTICIPATE!

QUESTIONS?