Planning and Running a Clinical Trial: Site perspective

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Declaration of Conflict Of Interest

I have the following potential conflict(s) of interest to report

Type of affiliation / financial interest	Name of commercial company
Receipt of grants/research support:	AstraZeneca, Bayer Healthcare, MSD, Resverlogix, KOWA, Pfizer
Receipt of honoraria or consultation fees:	Bayer Healthcare, MSD, Pfizer, Novo Nordisk
Participation in a company sponsored speaker's bureau:	Pfizer, Novo Nordisk

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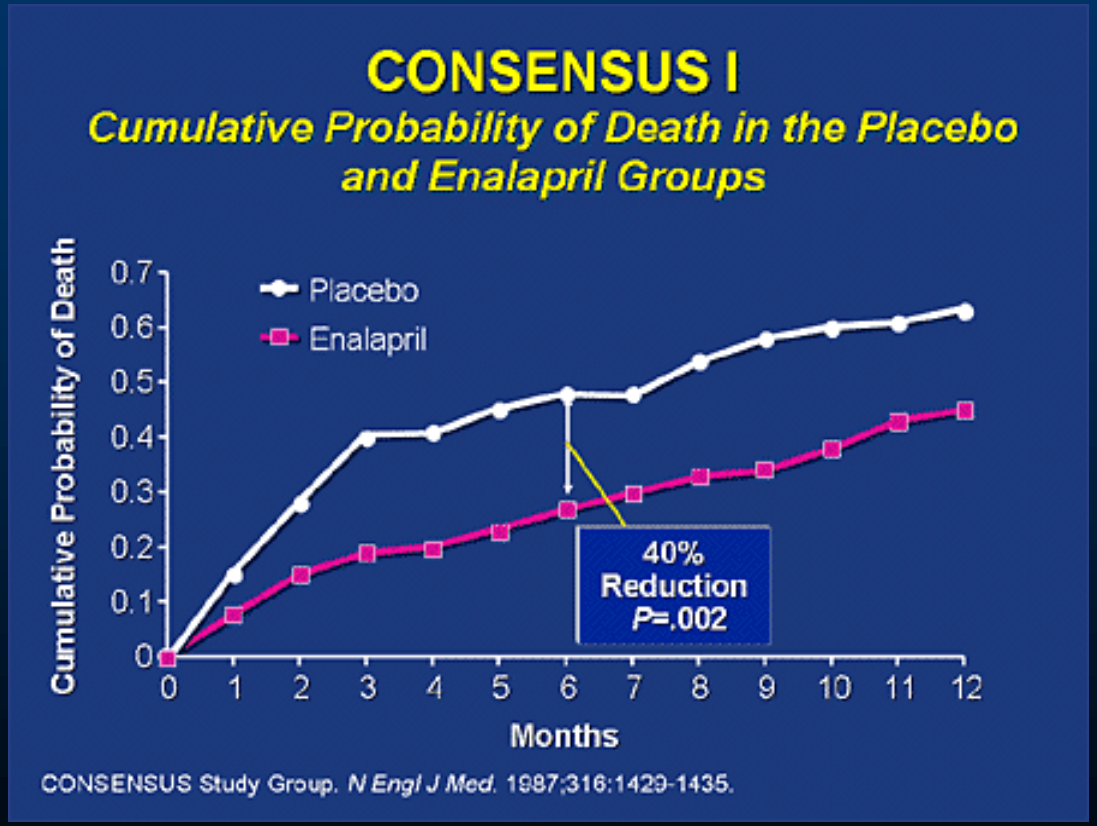
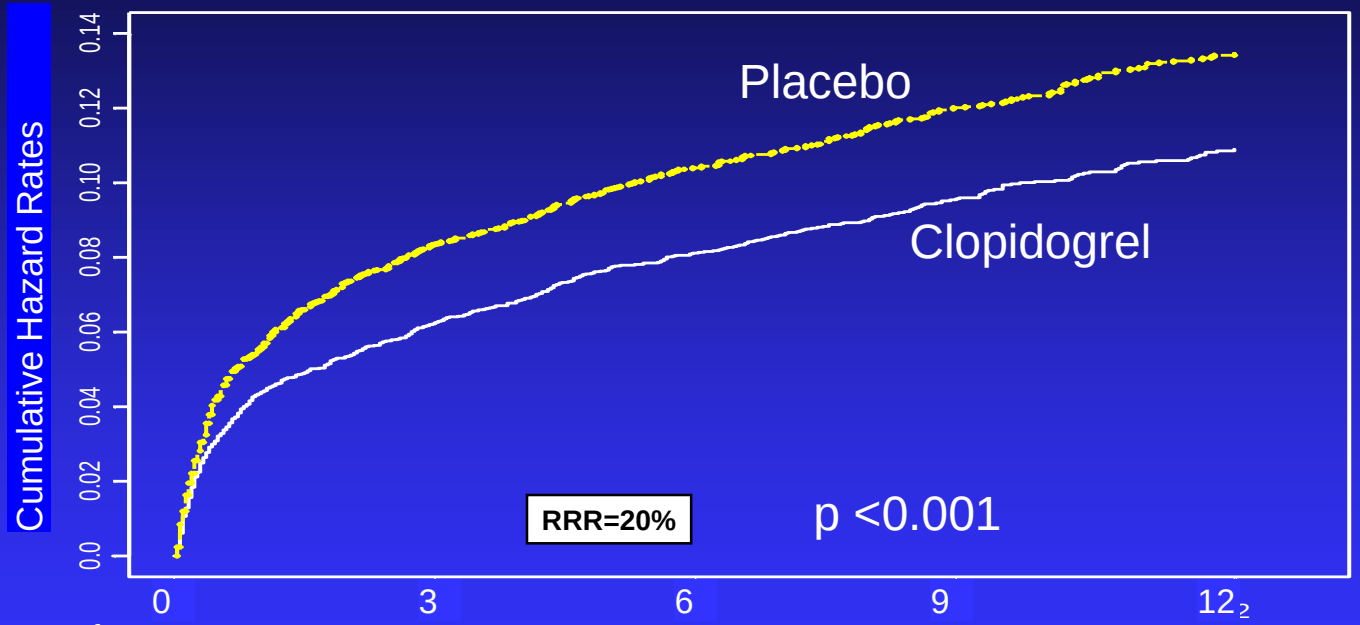
Trials that Changed Medicine: CHF



1987

ACS: Cumulative Hazard Rates for CV Death/MI/Stroke

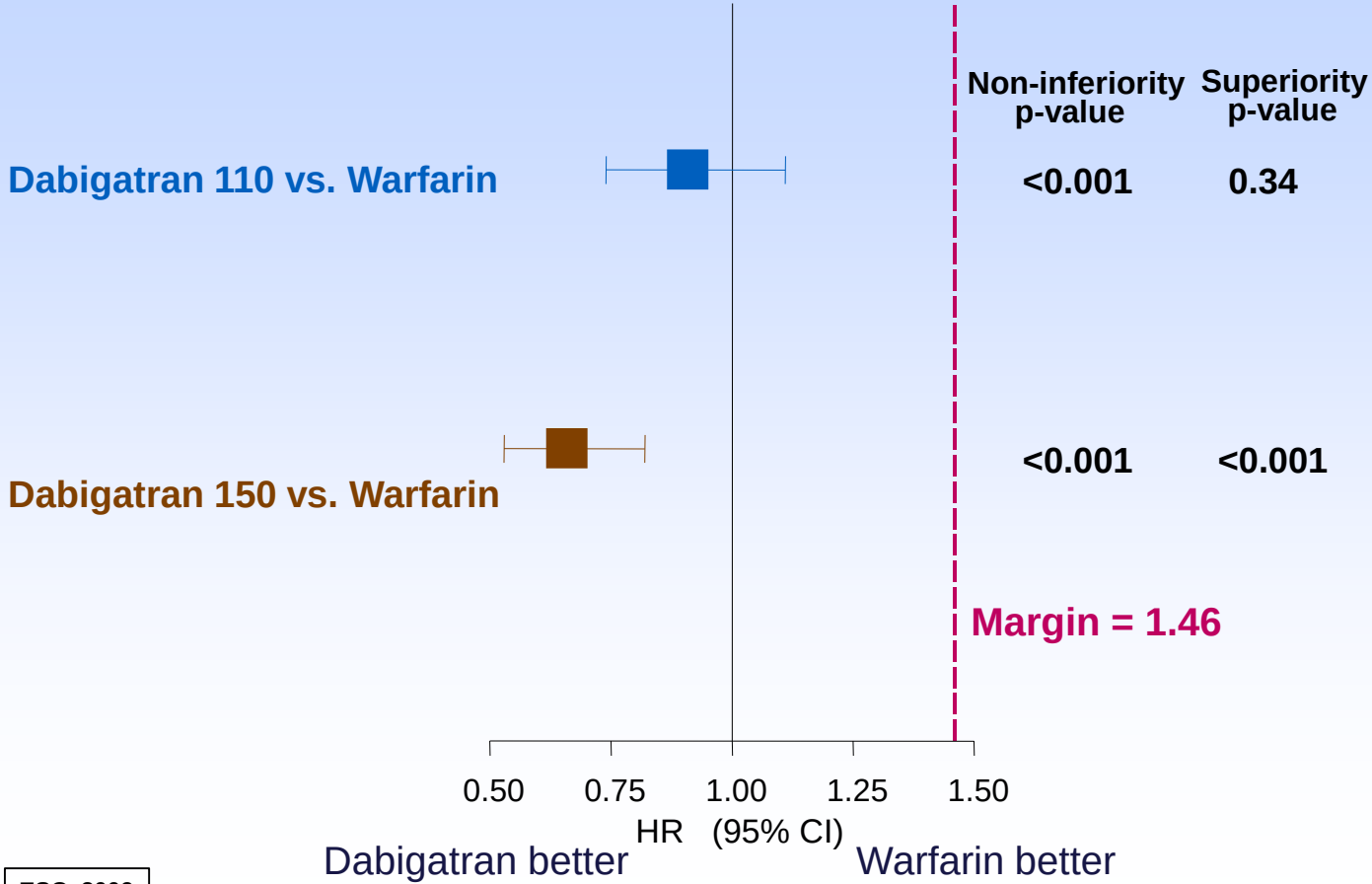


No of Pts					
Plac	6303	5780	4664	3600	2388
Clop	6259	5866	4779	3644	2418

ACC, Mar 2001

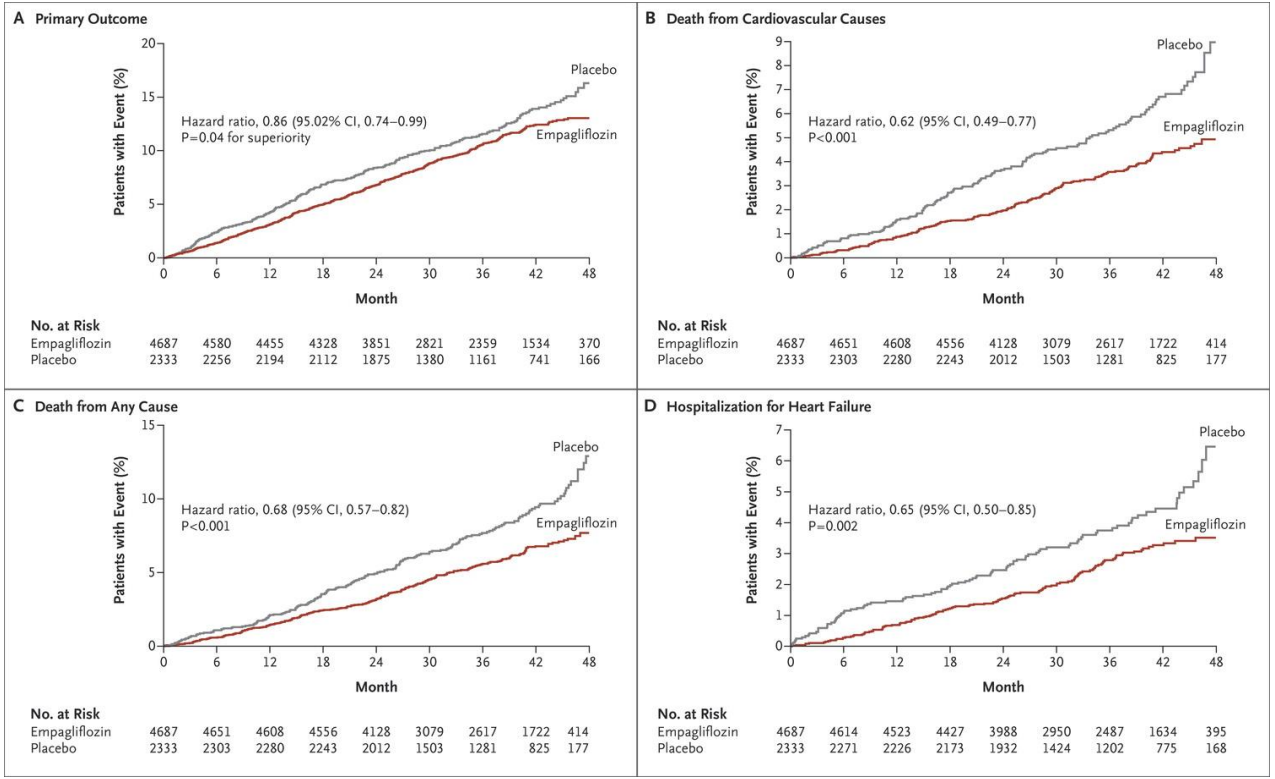
AF: Stroke or Systemic Embolism

RELY®
Study of stroke prevention in atrial fibrillation



ESC, 2009

EMPAREG: Effect of SGLT2 inhibition in Diabetes Mellitus



EASD, 2015

Trial Objectives –How did These Trials Succeed?

- **Objectives should be relevant and important**

- **Objectives should be clear and well defined**
  - Do ACE-inhibitors improve survival in HF patients?
  - Is DAPT superior to aspirin alone for reducing CV events?
  - Is dabigatran non-inferior to warfarin for preventing stroke/SE in pts with AF? And is dabigatran superior to warfarin?
  - Can antiglycemic drug choice impact on long-term outcome in DM patients?

The Site: PI and Research Team

- **PI**
  - MD with trial experience
  - PI is the lead scientist for a particular, defined research project, such as a laboratory study or clinical trial
  - PI may be at site level, or at country level

Duties of the PI During the Trial

- Check/sign informed consent sheets
- Check/sign CRFs (case report forms)
- Report SAEs and endpoints within 24 hours
- Read/sign safety report forms
- Take ample time for monitor visits
- Be prepared for audits (sponsor, local, government, international)
- **THE PI IS RESPONSIBLE FOR EVERYTHING IN THE TRIAL**

The Research Team

- Sub-investigators
  - Staff members, residents, trainees
  - All must have GCP training
  - Have delegated role in the trial, as specified by the PI
- Study Co-ordinators
  - Nurses
  - Biotechnicians
  - Other- social workers, other
- Administrative and secretarial support

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Residents and Trainees

Pros:

- **Early access to latest treatment strategies**
- **Access to top investigators and lectures**
- **Exposure to research methods**
  - Protocol, ICF, GCP
  - Criteria, definitions
  - Statistics plan
  - Attention to detail, CRF

Cons:

- **Less independent thought**
  - Done already by others
- **Less independent research and innovation**
  - Less time available
- **Less critical questioning**
  - Do as you are told!
- **Fewer publications**

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The Site: Must Have Adequate Facilities

- **Working space**
  - Team and monitors
- **Storage space**
  - Drug (IP), trial files, patient files
- **Storage facilities**
  - Store IP – Pharmacy? Research unit?
  - Refrigeration for IP
  - Refrigeration for biologic samples - -20? -80?
- **Equipment**
  - Routine equipment available - EKG, BP, scales, tapes, other
- **Local labs may be required**

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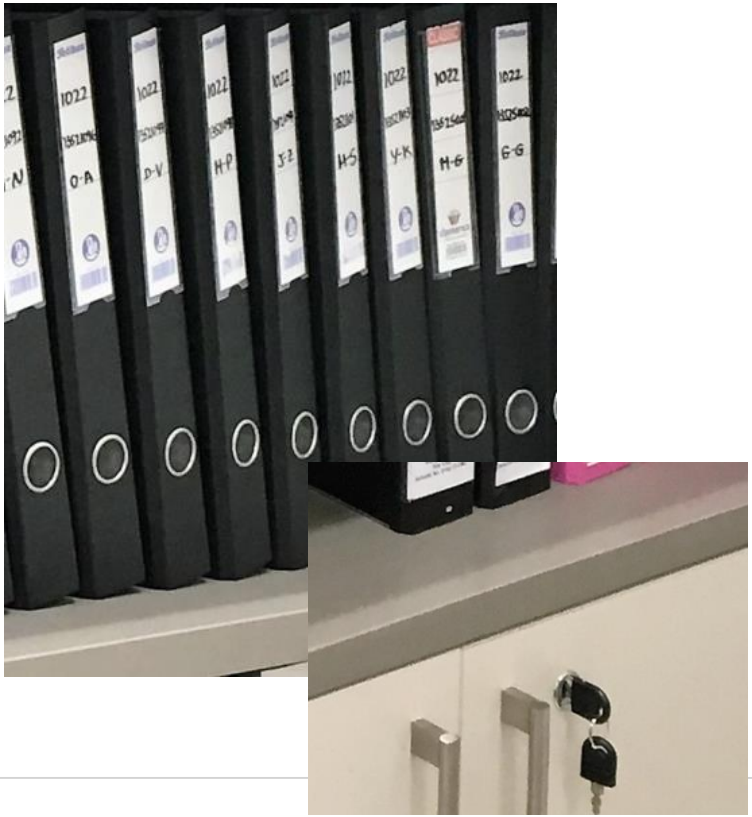
Trial Master File (TMF), Patient Records, Privacy



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Drug Storage, Lab Equipment

Temp-controlled centrifuges

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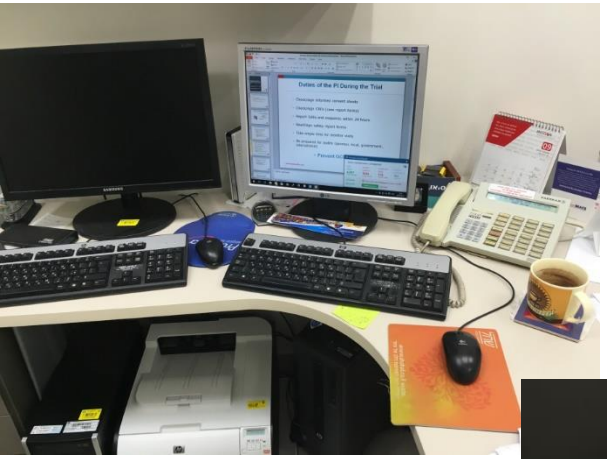
The Site – Administration and Communication

- **Electronic communication essential for most trials**
  - Email, fax, copiers, scanners
  - Web communication
  - CRF and data transfer usually depends on Electronic Data Capture (EDC)
  - Connection availability and speed (institutional firewalls can be challenging)

- **Site training**
  - All personnel need to be trained in communication with discreet user IDs

- **Paper based research trials for smaller/local trials**

A Well Equipped Office Complex



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The Site: Patients

- **Site should have access to appropriate patients**
  - Inpatient study (eg ACS, Acute HF)
  - Outpatient study (eg primary or secondary prevention)
  - Referral base
- **Enrollment expectations and commitment**
  - Realistic commitment
  - Competition for patients and resources must be taken into account
  - Track record
  - Financial viability

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Trial Procedures

- Identify the patient
  - Inclusion and exclusion criteria must be met, but more importantly, patient must have:
    - Understanding
    - Motivation
    - Availability for trial procedures and visit timelines
- Informed consent (ICF)
  - Do it correctly
  - Do it before any research dictated activities
  - Challenging when there are language issues
  - ICF errors are the commonest issues in FDA trial audits

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Trial Procedures

- Follow the Protocol
  - Record the findings
  - Dispense the treatment
  - Plan visit schedule
  - Update the CRF as soon as possible (4-5 days)

- Update the Family Practitioner and Record System
  - Letter to family practitioner
  - Documentation and trial info in patient record system

Clinical Trials: Ethics Committee

- The ethics committee (EC; IRB; “Helsinki” committee) is responsible for ensuring patient safety

- Composition of IRB
  - Scientists and researchers
  - Experts in the field
  - Pharmacists/pharmacologists (where relevant)
  - Institutional administrators
  - Public representative(s)
  - Legal opinion

Role of the Ethics Committee

The ethics committee is responsible for ensuring patient safety

- Ethics of the protocol
- Competence of the investigators and staff
- Informed consent language and process
- Ensure that there is an updated investigator brochure with proper information for investigators

Reviewing trial progress

- Number of patients in trial
- Adverse and serious adverse events
- Input from DSMB
- Protocol violations

Approval is usually renewable on an annual basis after review of trial progress

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Clinical Trials: Financing

- **Non- funded**
- **Institutional, health system funding**
- **Research grant**
- **Contract research with a sponsor**
  - Commercial entity or industry sponsored
  - Governmental or University sponsored

Role of a Clinical Research Organization

- **For most large-scale trials, a professional research organization is mandated by the sponsor to manage the trial**
  - Site selection and feasibility
  - Contracts
  - Submissions to IRBs
  - Initiation visits
  - Monitoring
    - Ensure data authenticity by checking source data
    - Ensure data completeness
    - Problem solving

Role of the Monitor

- **Monitoring is a method to ensure trial integrity**
  - Verify patient numbers
  - Verify compliance with trial protocol
    - Patient selection
    - Trial procedures
    - Event reporting
  - Verify storage and use of investigational product (IP)

- **Monitor may provide advice/assistance to site**
  - Interpretation of the protocol
  - Problem solving in cases of system malfunction (usually computer or shipping issues)

- **Monitoring level may vary**

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Role of the Monitor – Potential Issues

- **The monitor represents the CRO (and/or sponsor) and has conflicting motivation to that of the site team**
  - Defensive perspective
  - Motivation is beaurocratic rather than medical
  - CRO and sponsor are motivated by profit

- **NONETHELESS**

- ***Good working relationship between site and monitor is essential to the success of the project***

Adjudication (critical events committee, CEC)

- Adjudication ensures uniformity in interpretation of clinical events
- Adjudication can change outcome - but should not!
- Central or national?
  - National means no translations
  - Better understanding of local records and interpretation
- Total or partial?
  - Concordance rate between investigator and CEC?
  - Automated system can reduce load by more than 50%

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Patient retention

- **No patient ever leaves a trial**

- **Degrees of "compromise"**
  - Less drug or no drug
  - Fewer visits, more telephone
  - Less telephone contact? Once a year or end of study essential
  - Vital status should ALWAYS be sought – its in public domain

- **True total withdrawn consent – rare, in writing only?**

Consequences of Lost to Follow-up or Withdrawn Consent

2000 patients in trial

	Placebo	Active drug
	1000	1000
Event/dead	200	150

RRR = 25%, p=0.004

Lost to follow-up or withdrawn consent = 5% (50 each arm)

2000 patients in trial

	Placebo	Active drug
	1000	1000
Event/dead	200	150
Calc rate	200+0=200	150+50=200

RRR = 0%, NS

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How to Ensure a Successful Trial

- **Plan well in the beginning so that pts don't get lost**
  - ICF to allow tracking
  - Contact persons
  - E-treats and tricks inherent in study
- **Watch out for missed or late visits**
  - Reliability?
  - Drug supply problem
- **Motivate investigators and patients**
  - TCs, meetings
  - Patient groups – meetings and information

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