GCP and the EU directive in Primary Care

Dr. Amrit Takhar and Sister Jane Elwood

Web: www.wansford.co.uk

Programme - morning

- **Introductions and agenda setting**
- **Getting ready to host research in primary care**
- **Deciding to take part in a research study**
- **Roles and responsibilities of the primary care research team**
- **Different types of study and their implications for hosting**
- **Commercial/non commercial**
- **Eligibility,** Randomisation, Documentation

Programme - afternoon

- Monitoring visit requirements
- Event recording
- Adverse and serious adverse events
- Causality
- Links to PCT incident reporting
- New data during trial period & study completion tasks
- Delivering GCP training to practices
- Quiz
- Evaluation - what next

Programme

- Welcome and Introduction
- Importance of research
- Research Governance
- Team player roles
- Eligibility
- Event reporting, Study completion

Our Team

- Dr Amrit Takhar
- Jane Elwood
- Rachel Stainsby
- Dr Adi Shah (GP trainee)
- Alison Jackson
- Reception Team
- The Practice !!!

Recruitment to Clinical trials

Recent MRC studies

OPAL - Can n-3 fatty acids prevent age-related decline in cognitive function?

COMM-SYMPTOMS Common Symptoms in the community - understanding the publics responses in order to enhance appropriate care

ESCAPE Effectiveness of computer tailored Smoking cessation Advice in Primary Care: a Randomised trial

DVT-MAIN Air Travel and VTE main study

TOIB Are topical or oral Ibuprofen equally effective for the treatment of chronic knee pain in older people

Current portfolio activity

1. IID2 - recruited 100 patients into cohort study and 25 patients into GP presentation arm
2. ProCEED - Evaluation of a system of structured, pro-active care for chronic depression in primary care - Recruited 14 patients
3. Fluwatch - Influenza Pandemic Cohort
2007/08 10 Households with 20 participants

Current portfolio activity

5. MRC Diabetes – Questionaire – 20 participants
Improving the delivery of care for patients with diabetes through understanding optimised team work and organisation in primary care.

Current portfolio studies

6 ARRIVE STUDY - we have screened 35 patients and randomised 25
This is an industry sponsored portfolio study:
ARRIVE (Aspirin to Reduce Risk of Initial Vascular Events) is one of the largest clinical studies ever conducted in a population at moderate risk of initial events associated with cardiovascular and cerebrovascular disease (CVD).

Current portfolio studies

7. **OPEN STUDY (OLDER PEOPLE AND ENHANCED NEUOCOGNITIVE FUNCTION)**

The aim of this study is to assess whether increased dietary intake of crystalline vitamin B12 will improve nerve function and cognitive function in older people with defined low vitamin B12 status. Demonstrating that vitamin B12 dependant nerve and cognitive function impairment is present even in individuals without clinical symptoms will have considerable public health significance.

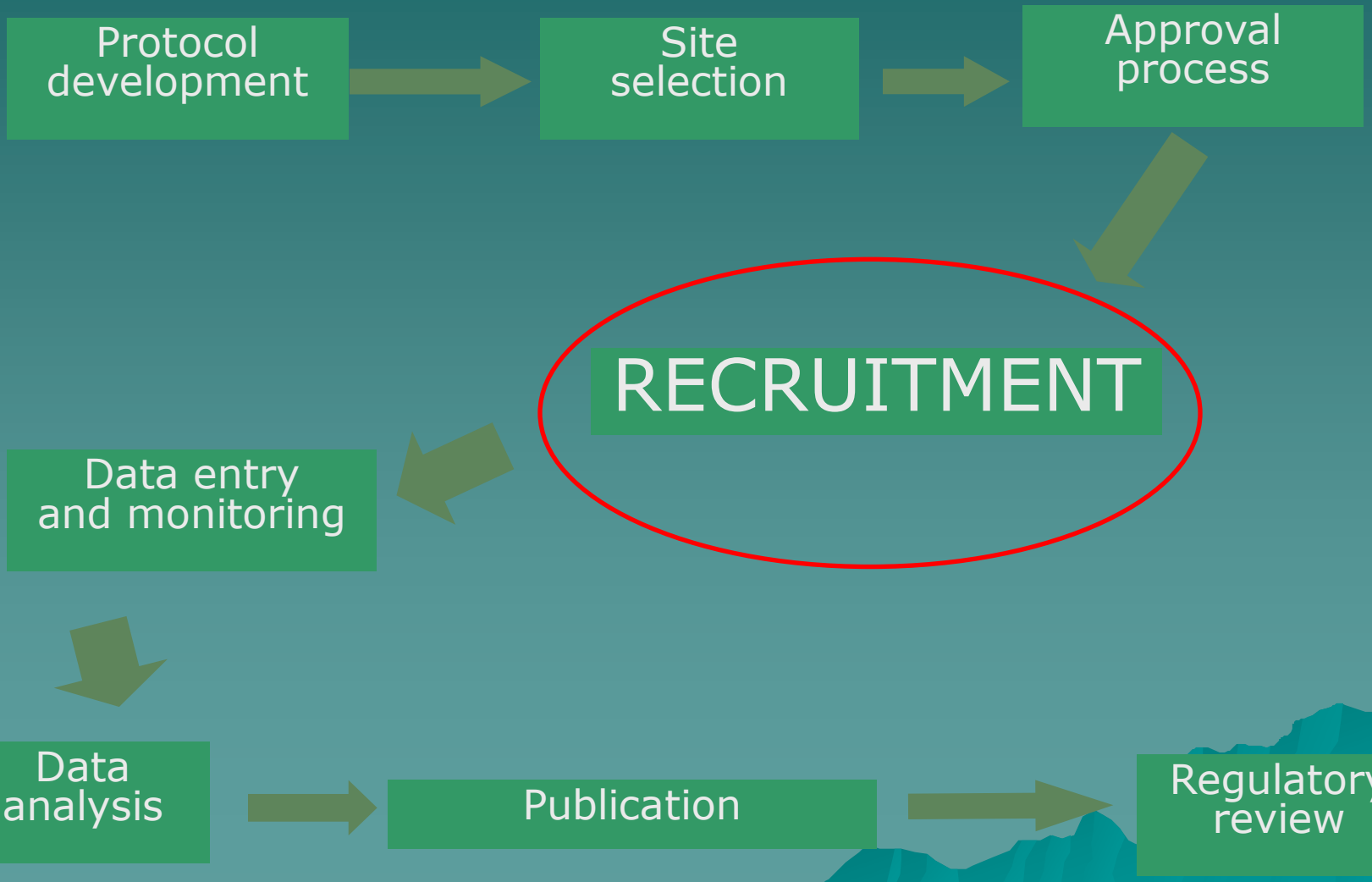
- To test this hypothesis, a randomised double-blind placebo controlled trial will be conducted on a cohort of 200 older people over 75 years of age at baseline.

Study Name	Status		Recruitment
Quintiles Venous leg Ulcers VALUE STUDY	Completed June2008	Observational	Complete – 6 patients completed
AMGEN Osteoporosis	Completed July2008	Observational	38 patients recruited
STUDY CLE – 12911 – 021 - PROTELOS "Observational cohort survey to evaluate the baseline profile of postmenopausal women treated for osteoporosis in current medical practice and the adherence and tolerability of patients treated with strontium ranelate during long-term follow-up "	Servier – 2 under surveillance	Observational April 2007 2 patients in 3 year survey finishing July2010	22 in survey, 2 in 3 yr study
Astra Zeneca Eurosmart/ Asthma	Recruitment complete	20 screened, 17 randomised	Complete by November 2008
Quintiles CONDOR – celebrex vs diclofenac/omeprazole	complete	May 2007	3 completed

Poet COPD- tiopropium vs salmeterol	**Recruiting**	**May 2008**	**4 recruited, target is 8**
Leo Facial Psoriasis - new ointment phase 3 trial	**Recruiting**	**Started May2008**	**12 recruited, Target is 8 Newspaper advert Posters in surgeries**
AstraZeneca - Saturn study - Patients on symbicort smart	**Recruiting**	**One year observational**	**5 recruited**
Merck HPV vaccine Extension **Protocol Title: A Long Term Immunogenicity, Safety and Effectiveness Study of GARDASIL™ (Human Papillomavirus [Types 6,11,16,18] Recombinant Vaccine) Among Adolescents Who Received GARDASIL™ at 9-18Years of Age**	Recruiting	10 year study	5 planned in extension study – extends follow up to 10 years
Optimise study – Diabetes Astrazeneca OPTIMISE: Optimal Type 2 Diabetes management including benchmarking and standard treatment.	Recruiting	One year observational – doctor group	12 recruited – maximum allowed 12

Studies awaiting approval or being considered			
Tinnitus – new drug , phase 3	Awaiting appoval	New oral drug	
Severe dandruff phase 3 trial Dermal KSA-03	Awaiting approval	New topical agent	
Novartis hypertension study	Feasability	New combination drug	

Clinical trial processes



History

- Nuremberg trial
- Declaration of Helsinki 1964
- ICH GCP 1996
- EU directive

"The voluntary consent of the human subject is absolutely essential"

Medicines act 2004

- Medicines for Human Use

(Clinical Trials) Regulations 2004

- Compliance with GCP is now a legal obligation in UK / Europe for all trials of investigational medicinal products

Good Clinical Practice

AIM : Protection of human subjects and assurance of credible data

Compliance… provides public assurance that the rights, safety and wellbeing of trial subjects are protected

Research Ready

What are the benefits from doing Research ready?

Successful completion of the self-accreditation will lead to your practices' inclusion in our database of Research Ready accredited practices.

A practice that is Research Ready accredited will be:

Aware of what participating in research entails.

Aware of the regulatory context in which research activity has to be undertaken.

Aware of the responsibilities placed upon the practice and its individual members of staff.

Aware of how it can minimise any potential risks for the practice, practice staff and study participants.

Assured that the practice is meeting the required standards.

Able to benefit from the formative aspects of the self-accreditation and use these to develop their expertise.

Plus:

An annual system of reaccreditation ensures that practices keep themselves up to date with the constantly changing world of research governance and that their details on the Research Ready database remain accurate.

The Research Ready file provides a useful reference for the research team and also for the induction and training of new staff in the practice who will be participating in its research activities.

The opportunity to be involved in a wider range of research projects.

Feel good factor – staff in the practice can congratulate themselves on their knowledge!

Research Ready

There are 5 Core Competencies within the specific criteria:

Is there support within the practice for research activity? (1 essential criterion)

Does the practice have identified space and facilities to host research? (5 essential criteria and 7 clinical trials criteria)

Can searches of the practice database be carried out? (3 essential criteria)

Do you know what is required of your practice and individual members of staff with reference to research governance? (Research Governance Part 1) (9 essential criteria and 1 clinical trials criterion)

Are you aware of the responsibilities you have to your patients and staff if they are participating in research studies? (Research Governance Part II) (12 essential criteria and 2 clinical trials criterion)

Research Ready

You can add documents that support your answers, such as policies, research agreements or other relevant information you may have downloaded as your practice progresses through the assessment.

As Research Ready File develops it will gather together information that will be helpful for the induction or training of staff with research responsibility in your practice, or for existing staff to refresh their knowledge if necessary and it should be readily accessible to all those participating in the self-accreditation within your practice.

Answers can be saved at any stage of the self-accreditation process so that all members of the 'research team' can independently contribute to its completion. This also provides the opportunity for your Lead Researcher to review the information provided and for it to be accessed by all of the staff involved in completing the assessment. Adopting this working method will ensure that research knowledge is shared amongst the team. It is also possible that by working in this way you will become aware of practice policies etc. that would benefit from updating/amending!

Information for participants

- What is the research for?
- What happens to participants?
- Anticipated effects
- Risks
- Whom to contact if problems

All in a format they can understand

Patient reasons to do trials

- Access to study drug not otherwise available to them
- Access to tests not otherwise available to them
- Value the extra time available
- Like the ‘full MOT’
- True altruism
- Better supervision of their condition (more intensive) – patients in trials have better outcomes
- Social therapy

Information for clinicians

- Research protocol (including named PI)
- Information given to participants
- Allocation details when they are known
- Clinical course of this patient
- Test results
- Overall results of study

Research in Primary Care

- Pharmaceutical Drug Trials
- Academic Studies through Universities
- Medical Research (MRC)
- Local Research Networks
- Our own research
- Masters, Ph D students

Good Clinical Practice

AIM : Protection of human subjects and assurance of credible data

Compliance… provides public assurance that the rights, safety and wellbeing of trial subjects are protected

Good Clinical Practice

- An international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects.

WORLD MEDICAL ASSOCIATION Declaration of Helsinki

- Clinical trials should be conducted in accordance with the Declaration of Helsinki…
  - *ICH GCP 1997*
- The accepted basis for the conduct of clinical trials in humans is founded in the protection of human rights….as reflected in the 1996 Helsinki Declaration
  - *EU Clinical Trial Directive 2001*

Declaration of Helsinki – Key Elements

- Protection of patients rights
- Informed consent
- Independent approval
- Scientific / Medical basis
- Appropriate risk benefit
- Subject well being takes precedence over other considerations

ICH

- International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

We need to Demonstrate

- We are qualified to do the job.
- Knowledge of GCP and Regulatory Requirements
- The appropriate patients for the study.
- Time and Staff numbers
- Space

What is Research Management and Governance?

- Application of principles to health and social care research to ensure public confidence in research
- Research Governance helps to optimise the quality of research by
  - Enhancing ethical and scientific quality
  - Promoting good practice
  - Reducing adverse incidents and ensuring lessons are learned
  - Preventing poor performance and misconduct

Five Aspects to RM&G

- Finance
- Information
- Science
- Health & Safety
- Ethics

RM&G mirrors the aims of GCP

International ***ethical and scientific quality standard*** for designing, conducting, recording, and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the ***rights, safety and well-being of trial subjects are protected***, consistent with the principles that have their origin in the Declaration of Helsinki, and that the ***clinical trial data are credible***

The links between the two:

- GCP lists all essential documentation for the conduct of a trial. This includes all the appropriate approvals:
  - Ethics (must be GCP compliant)
  - MHRA (regulatory for medicinal products)
  - AND Local NHS trust approval (RM&G)

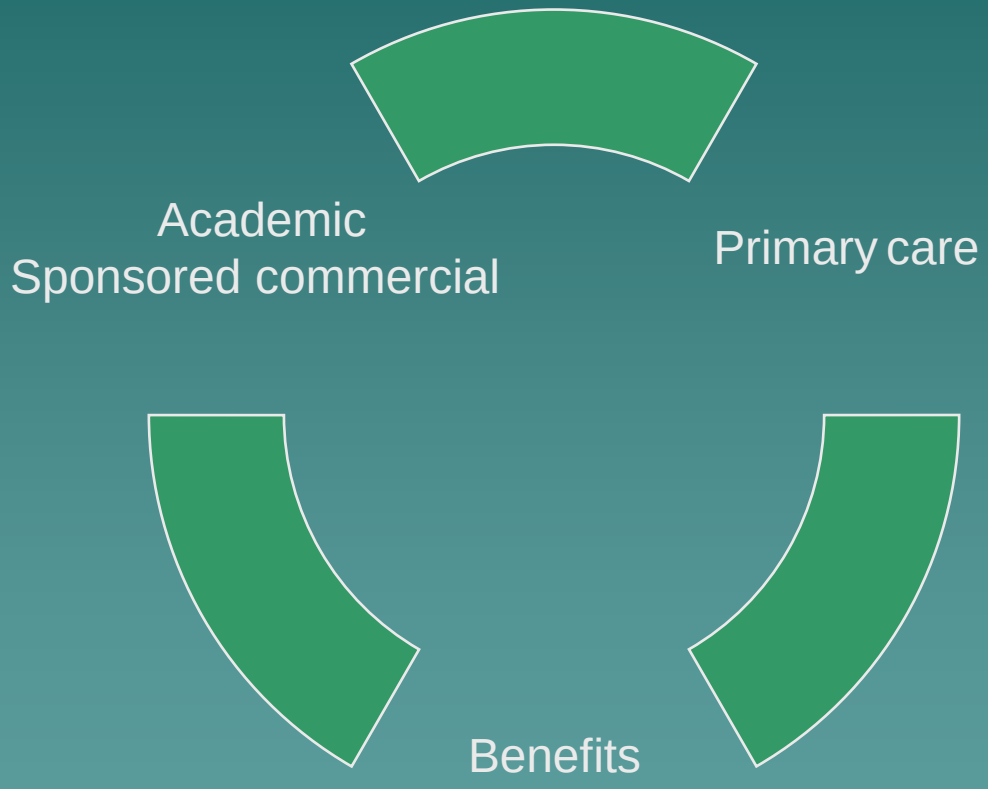
And on the flip side

- RM&G requires the principles of GCP to be adhered to:
  - Research Governance Framework for Health and Social Care (DOH 2005)
  - Terms of conditions of Cambridgeshire and Peterborough PCT Governance review.
    - All principle local researchers and their research teams should be trained in and comply with the principles of GCP.

RM&G – GCP summary

- RM&G is not just an approval required from Trusts… it goes further
- GCP is a set of international standard principles
- RM&G and GCP are intertwined.
- The principles of GCP apply to all research involving patients
- Not just a legal obligation – it is good research practice.

We need them/They need us



Exclusion Criteria

Is pregnant or lactating

Is a woman of childbearing potential not using an effective method of birth control

Has shown hypersensitivity to compounds similar to the trial drug

Has shown hypersensitivity to compounds similar to the trial drug

Has no history of asthma or GI problems

Is taking any contra indicated medications such as Ketoconazole, Itroconazole, Erythromycin

Has participated in a clinical trial using any new investigational drug within the last 3 months

SUBJECT ELIGIBILITY EXERCISE EVALUATION

If you selected to include the subject:

You review the criteria with the subject and decide to **include** her.

Yes the subject does fit the eligibility criteria and therefore is able to enter the study. It is very likely that she completes the study with no adverse events **BUT** are there any considerations that you may take into account?

If you selected to exclude the subject:

You review the criteria with the subject and decide to **exclude** her. Technically the subject fits the entry criteria **BUT** there may be good reasons to reconsider this subject.

For both options: If you are one of a group of Primary Care Physicians in a larger practice, do you see any areas which may lead you to prevent this subject entering the study?

You review the criteria but during the study period the subject develops a Upper Respiratory Tract Infection (URTI). You are away when she visits the surgery and your partner prescribes Erythromycin. The subject develops a shortness of breath and bouts of dizziness. This is reported as an adverse event. This is a protocol violation. More importantly the symptoms indicate that the Erythromycin may have altered the metabolism of Terfenadine which results in Torsales de Pointes (TdP) due to prolongation of the QT interval which could result in the death of the subject.

Would you still enter this subject on the study given the possible outcome?

In this case the protocol was not followed therefore any indemnity offered by the Sponsor Company is invalid and you be deemed negligent. This extreme example demonstrates the importance of the inclusion/exclusion criteria and also the importance of ensuring there is clear communication and everyone is aware of any clinical trial ongoing in their unit and the requirements.

Problem Areas / Consent 1

- Minors
- Incapacitated Adults (eg Unconscious)
- Non English Speaking
- Illiterate
- Vulnerable Subjects. (Dementia)

Problem Areas /Consent 2

- Use language compatible with their understanding.
- Require a legal representative/Carer to consent in their stead.
- Impartial Witness if both subject and carer are illiterate.
- IF IN DOUBT DO NOT ENROL

Causality according to PI

- AE Adverse Event
- ADR Adverse Drug Reaction
- SAE Serious Adverse Event
- SUSAR Suspected Unexpected Serious Adverse Event
- Code Break may be requested.
- In Academic Studies 3rd party breaks code

Users and participants expect that:

- Money will not be wasted or stolen
- Research will address questions that matter
- Research will be scientifically sound
- Participants will be told what's going on
- No-one will get hurt
- Data will be treated as private
- Results of research will be made public

What is research?

"Research can be defined as the attempt to drive generalisable new knowledge by addressing clearly defined questions with systematic and rigorous methods."

DoH Research Governance Framework

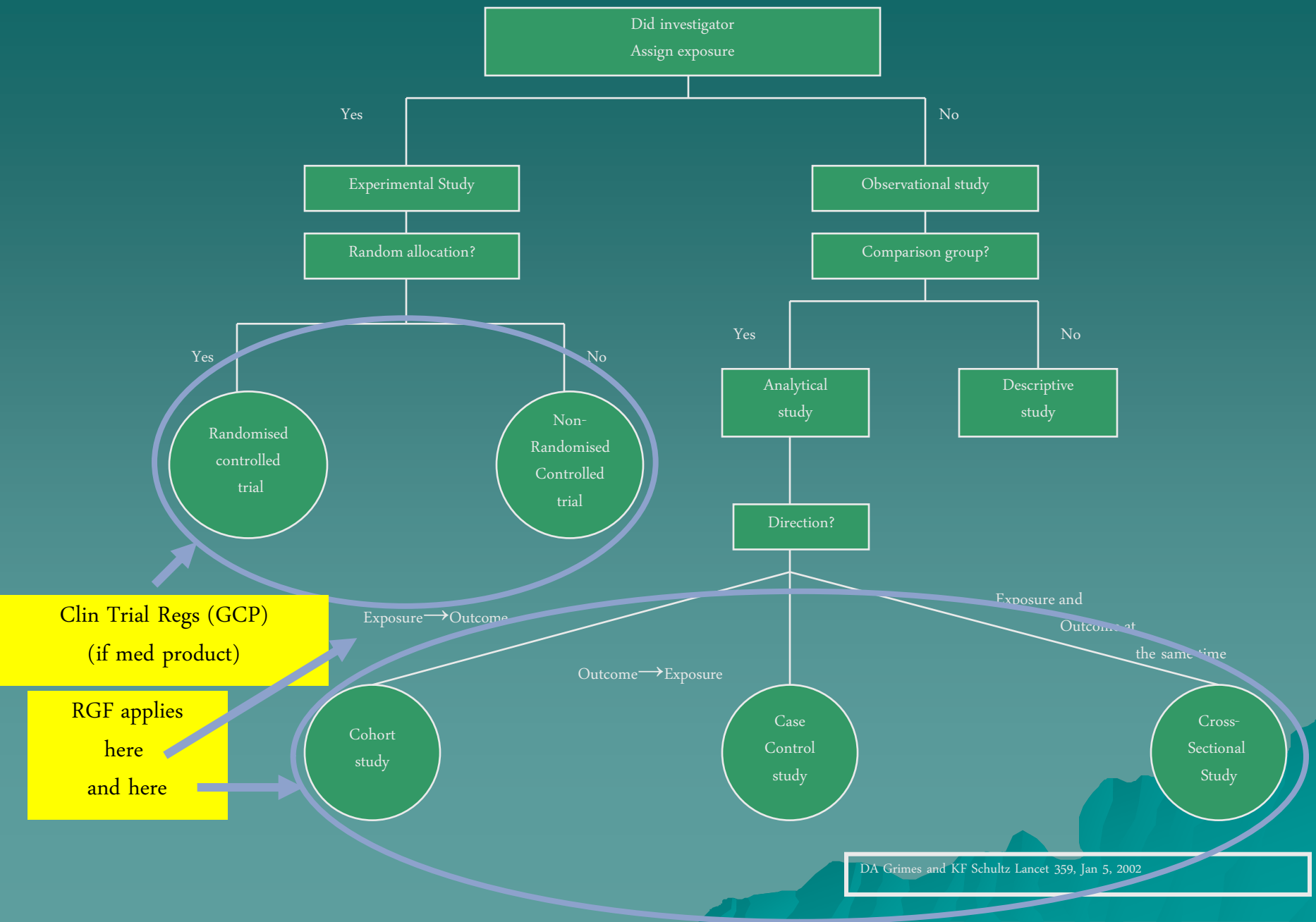
Definition of Clinical Trial

'any investigation in human subjects intended to discover or verify the **clinical, pharmacological and/or other pharmacodynamic effects** of one or more **investigational medicinal product(s)**, and/or to **identify any adverse reactions** to one or more investigational medicinal product(s) and/or to **study absorption, distribution, metabolism and excretion** of one or more investigational medicinal product(s) with the object of **ascertaining its (their) safety and/or efficacy**.'

Definition of Investigational Medicinal Product

'a pharmaceutical form of an **active substance or placebo** being tested or used as a **reference in a clinical trial**, including products already with a marketing authorisation but used or assembled (formulated or packaged) in a way **different from the authorised form**, or when used for an unauthorised indication, or when **used to gain further information about the authorised form**'

Classification of the Types of Clinical Trial



DA Grimes and KF Schultz Lancet 359, Jan 5, 2002

Factors affecting recruitment

- Trial availability
- Patient population
- Trust in researcher
- Staffing
- Infrastructure
- External factors
- Ease of recruitment

Managing workload impacts recruitment

- Trial setup, meetings, protocol review, approvals
- Assessing capacity and personnel
- Screening and consent
- Data queries
- Electronic CRF vs paper
- Monitoring visits

Practice reasons to do trials

- Quality
- Innovation-lead the way
- Financial
- Status
- Service to patients

Operating procedures - recall

- Database search
- Write to suitable patients
- Follow up phone call
- Detailed information (PIL) sent to those interested
- First appointment booked for informed consent
- Deadlines and performance pressure ++
- Quality checks (monitoring)
- Document each stage of the process in medical record

Operating procedures - opportunistic

- Potential research participant identified by practice member
- Brief information given
- Detailed information (PIL) to those interested
- Telephone followup by research department
- First appointment booked for informed consent
- Document each stage of the process in medical record

Challenges that face us

- Trials are not an easy option and they are getting tougher
- Legal issues
- Business pressures
- Variations between companies-5 different ways to write the date for example!
- Cash flow
- Electronic data entry – eCRF and remote monitoring
- Practice involvement – reminders

Challenges that face us during trials

- Pressure to achieve targets-competitive recruitment
- Protecting patient rights e.g. recruitment 'closed', patients doing trials for the wrong reasons
- Escalating documentation
- The computer…a mystery to most
- Changing regulations – ethics and govenernace approvals
- Cross boundary issues

Challenges

- Maintaining staffing levels when activity slows down
- Costing trials when limited protocol information available
- Monitoring and data queries
- Time pressures
- Policies and SOPs

Recruitment to trials – critical success factors

- GP motivation
- Research training and skills
- Practice support and capacity
- Funding and time
- Infrastructure setup costs in practice – admin support and record keeping
- Seeking research funding
- Approval and registration

Raising the profile of research

- In house meetings
- Newsletters
- Media advertising
- Regional Network links
- Patient groups
- PCT support

Patient involvement

- Open day
- Newsletters, articles
- Satisfaction questionnaire
- Regional Network links
- Patient group liaision
- Research events

Barriers to recruitment

- Lack of ownership and commitment
- Major knowledge and skills gaps
- Conflicting priorities and no protected time
- No protected funding for research infrastructure
- Poor physical space, IT systems near-obsolete or not used
- Lack of experience

Quality research culture

- Respect for the dignity, rights, safety and well-being of research participants
- Valuing diversity (not ageist, racist etc)
- Personal and scientific integrity
- Leadership
- Honesty, accountability and openness