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Standards for Data and Statistics in the Regulation of Medicines

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How is cancer treated?

- Surgery
- Radiotherapy
- Chemotherapy
- Hormone treatments
- Monoclonal antibodies….

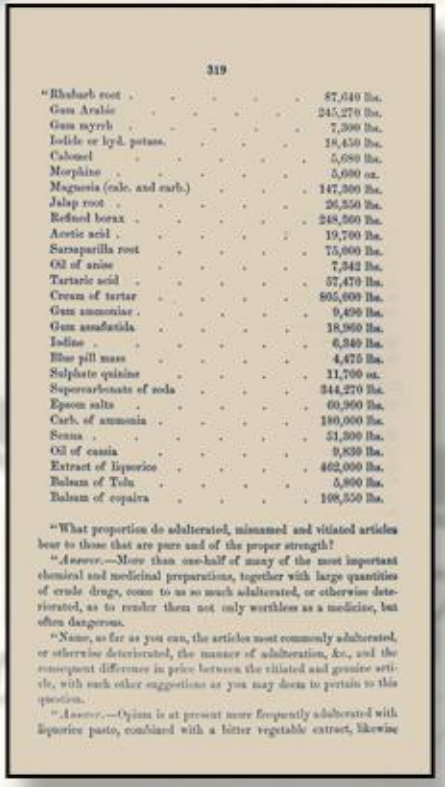
- How do we know they work and are safe?
- How do we know we can trust the evidence?

THE HISTORY of DRUG REGULATION

- **Ensure the safety and effectiveness of medicines**
- **Respond to public health disasters**

1848

IMPORTED DRUGS



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"Rhubarb root	87,640 lbs.
Gum Arabic	245,270 lbs.
Gum myrrh	7,300 lbs.
Iodide or ly'd. potass.	18,450 lbs.
Calomel	5,680 lbs.
Morphine	5,600 oz.
Magnesia (calc. and carb.)	147,300 lbs.
Jalap root	26,350 lbs.
Refined borax	248,360 lbs.
Acetic acid	19,700 lbs.
Sarsaparilla root	75,800 lbs.
Oil of anise	7,342 lbs.
Tartaric acid	57,470 lbs.
Cream of tartar	895,600 lbs.
Gum ammoniac	9,490 lbs.
Gum assafœtida	18,960 lbs.
Iodine	6,340 lbs.
Blue pill mass	4,475 lbs.
Sulphate quinine	11,700 oz.
Supercarbonate of soda	344,270 lbs.
Epsom salts	60,900 lbs.
Carb. of ammonia	180,000 lbs.
Senna	51,300 lbs.
Oil of cassia	9,830 lbs.
Extract of liquorice	462,000 lbs.
Balsam of Tolu	5,800 lbs.
Balsam of copaiva	108,350 lbs.

"What proportion do adulterated, misnamed and vitiated articles bear to those that are pure and of the proper strength?

"Answer.—More than one-half of many of the most important chemical and medicinal preparations, together with large quantities of crude drugs, come to us so much adulterated, or otherwise deteriorated, as to render them not only worthless as a medicine, but often dangerous.

"Name, so far as you can, the articles most commonly adulterated, or otherwise deteriorated, the manner of adulteration, &c., and the consequent difference in price between the vitiated and genuine article, with such other suggestions as you may deem to pertain to this question.

"Answer.—Opium is at present more frequently adulterated with liquorice paste, combined with a bitter vegetable extract, likewise

- **Prohibited the importation of unsafe or adulterated drugs**
- **Ineffective because of enforcement challenges and domestic patent medicines**

1906

LABELING DRUGS

- **1906 Pure Food and Drugs Act**
  - **Prohibited interstate commerce of unsafe drugs**
  - **Required proper labeling**
  - **Identified official standards for drugs**

1938

DRUG SAFETY

- **The Food, Drug, and Cosmetic Act of 1938**
  - **Required proof of safety**
  - **Authorized inspections**
  - **Outlawed false claims**

1962

DRUG EFFICACY

- **Calls for revisions of the drug laws**
- **Thalidomide disaster**

1962

DRUG EFFICACY

- **The Kefauver-Harris Amendments of 1962**
  - **Required proof of effectiveness**
  - **Gave FDA control over investigations**
  - **Gave FDA authority to regulate advertising of prescription drugs**
  - **Established good manufacturing practices**

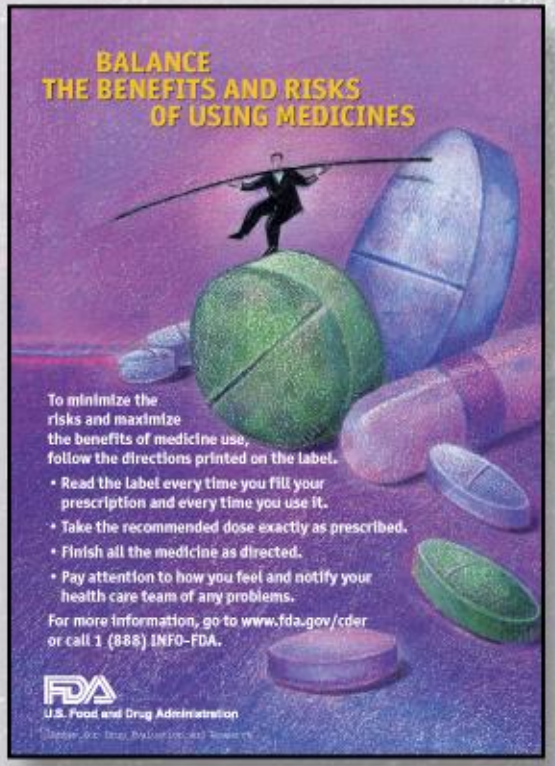
DRUG LABEL EVOLUTION I

- Early labels decorative
- Drug labels today
  - Indications
  - Dosage
  - Possible interactions
  - Other information

DRUG APPROVAL in the 1990's

- **Standard drug testing and approval process**
  - **Preclinical testing**
  - **Clinical studies – Phase I, II, III**
  - **Postmarketing surveillance**

DRUG APPROVAL in the 21st CENTURY



- **FDA adopts science of risk management**
  - **Identification of risks**
  - **Balance of risks and benefits**
- **All drugs have risks**

FOR MORE INFORMATION VISIT

MILESTONES
in
U.S. DRUG LAW HISTORY

www.fda.gov/cder/centennial/default.htm

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A Brief History of Statistics in Drug Regulation

- 1964 Medicines Act
- 1991 RSS Report “Statistics and Statisticians in Drug Regulation in the United Kingdom” (including discussion of the EC CPMP, due in 1992)
- 1994 First statistician, John Lewis, appointed to MCA (now MHRA)
- 1998 ICH-E9 Statistical Principles for Clinical Trials

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A Brief History of Statistics in Drug Regulation

2020

- MHRA Statistics Unit thriving
- Statisticians on CHM and EMA committees and secretariats
- ICH-E9 still going strong, but new thinking and multiple guidelines on statistical issues to meet emerging challenges

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ICH E9 statistical principles for clinical trials

- First issued 1998
- focus on statistical principles
- addresses key design, conduct, analysis and reporting issues
- NOT a prescriptive approach

- supplemented in 2020 by
- ICH E9 (R1) addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials

Academically run trials

Clinical trials are the gold standard for the evaluation of new treatments/interventions in healthcare

- Provide evidence to improve clinical service

Clinical trials require multidisciplinary team science

- Clinicians, allied health professionals, statisticians, trial and data management, quality assurance, health economics, qualitative researchers

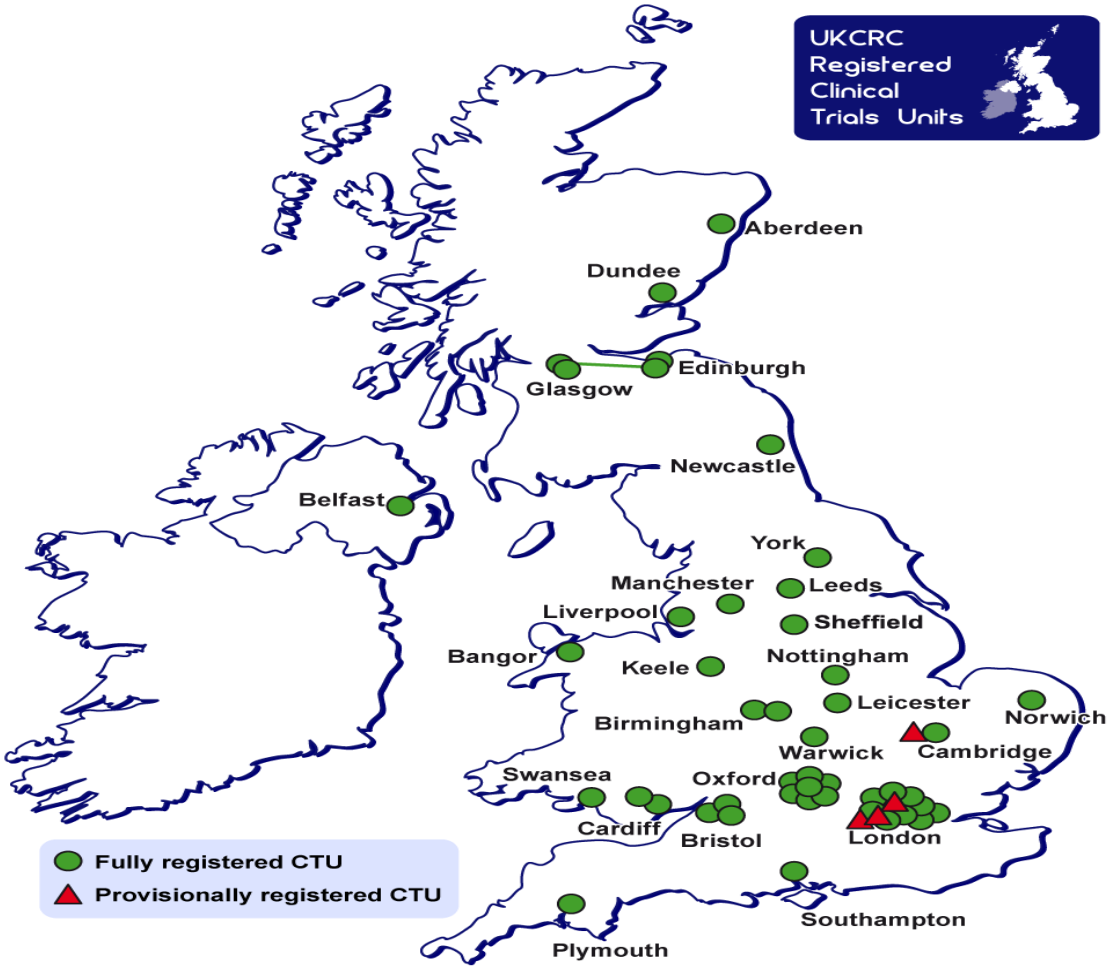
Clinical Trials Units – Multidisciplinary Team

- Clinical Trial Methodologists
- Financial grant planning and administration
- Health Economics
- Information Systems
  - Data base design, management, randomisation, remote data capture
- Patient Public Involvement
- Qualitative research
- Quality assurance
- Site Monitoring
- Statistics
- Trial and data management

UKCRC Registered CTUs

- 49 Registered CTUs across UK
- International Review Panel assess competency every 3 years
- Recommendations endorsed by UKCRC Board
- Key competencies:
  - Knowledge, track record of design, conduct and analysis of multicentre clinical trials
  - Established multidisciplinary team including stats, trial management, IT
  - Robust QA systems with SOPs in essential areas
  - Robust and secure IT systems
  - Systems for Risk Assessment to guide appropriate monitoring
  - Secure randomisation system

Network of 49 UKCRC Registered CTUs



Trial Stages and CTU Provision of Support

- Grant prep
- Study hypothesis
- Study Design
- Sample Size
- Study Protocol
- Feasibility
- Outcomes/outcome development
- Costings

- Consent Form
- Protocol Development
- Case report Forms
- Database design
- Randomisation
- Ethical approval
- Administrative registration
- Logistics
- Study Centres

- Trial management
- Coordination
- Adverse event management
- Randomisation
- Monitoring
- Trial meetings
- Quality assurance

- Statistical analysis plan
- Data validation
- Programming and analysis

- Study Reports
- Data interpretation
- DMEC reports
- Trial Steering Committee reports
- Archiving

- Advice and consulting
- Scientific writing

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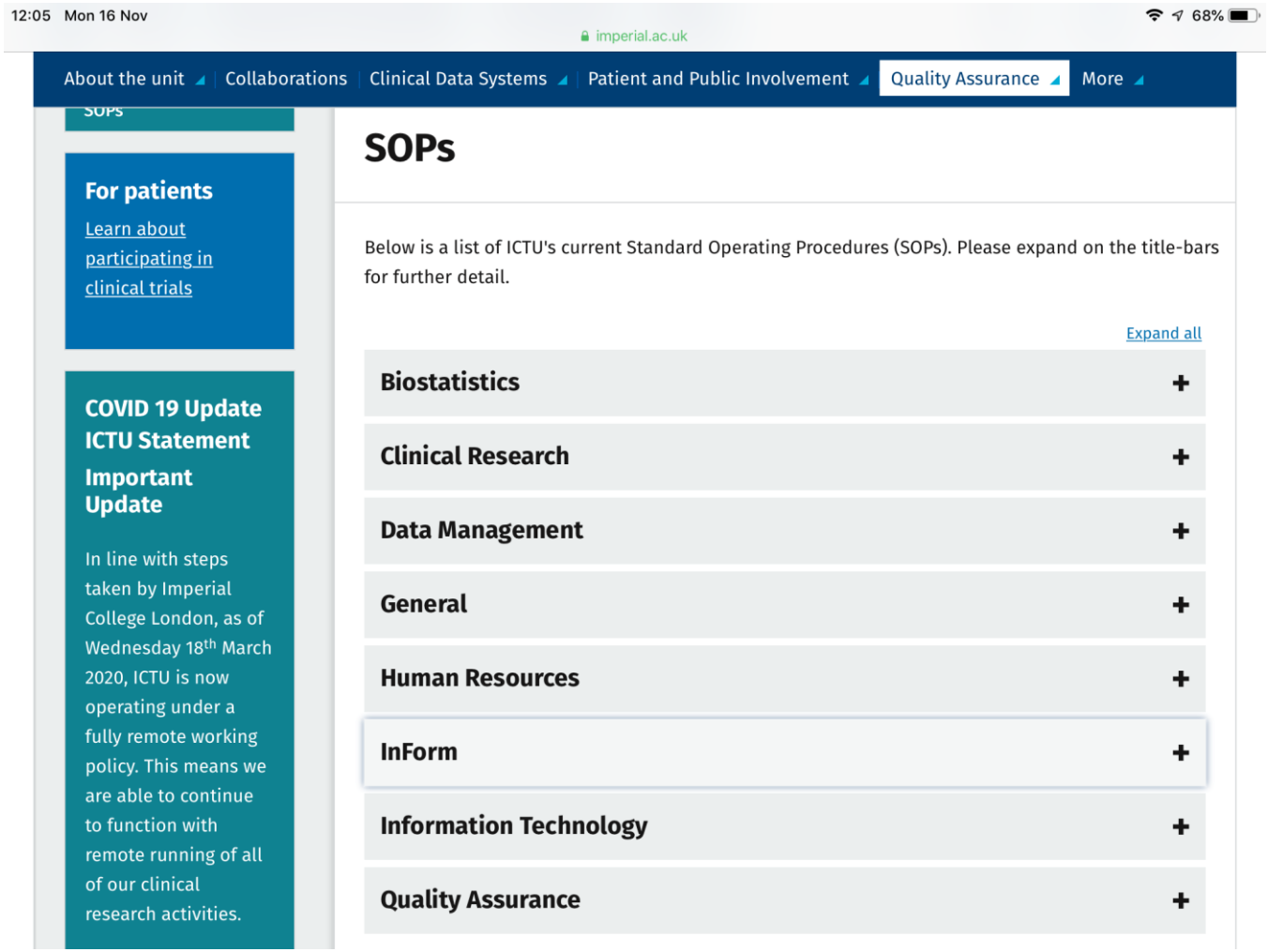
ICTU SOPs



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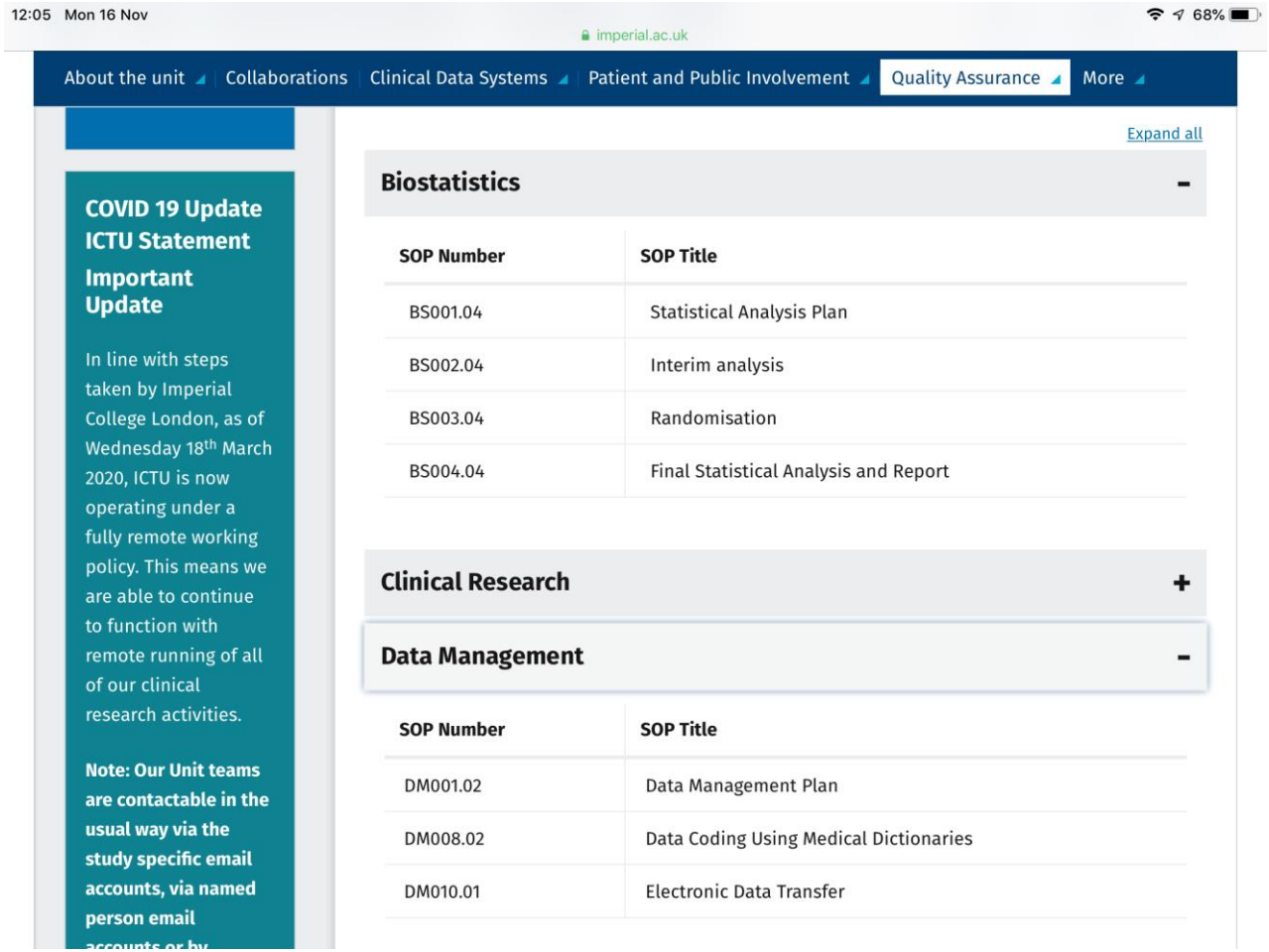
ICTU SOPs



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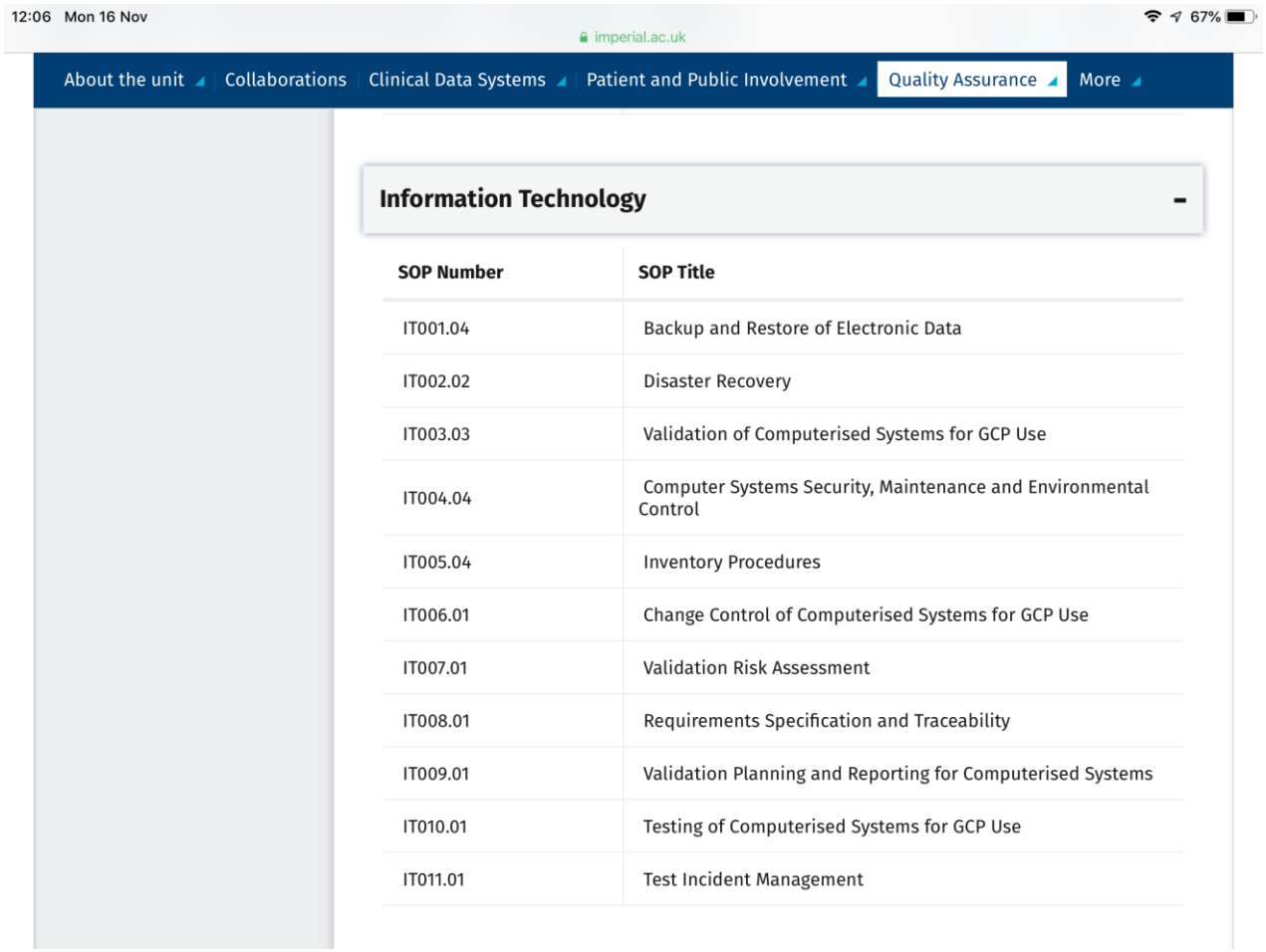
ICTU SOPs



Information Technology

SOP Number	SOP Title
IT001.04	Backup and Restore of Electronic Data
IT002.02	Disaster Recovery
IT003.03	Validation of Computerised Systems for GCP Use
IT004.04	Computer Systems Security, Maintenance and Environmental Control
IT005.04	Inventory Procedures
IT006.01	Change Control of Computerised Systems for GCP Use
IT007.01	Validation Risk Assessment
IT008.01	Requirements Specification and Traceability
IT009.01	Validation Planning and Reporting for Computerised Systems
IT010.01	Testing of Computerised Systems for GCP Use
IT011.01	Test Incident Management

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Good Clinical Practice

- Good Clinical Practice (GCP) is the international ethical, scientific and practical standard to which all clinical research is conducted
- GCP protects the rights, safety and wellbeing of study participants
- Required to do training every two years- GCP courses abound, both face-to-face and online

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Data standards- CDISC

- “Adopting CDISC standards is an invaluable investment that leads to more meaningful, more efficient research for your organization and the entire global research community. Implementing standards to collect, structure, and analyze data makes it easier for you to aggregate information and take advantage of big data and helps ensure your data is accessible, interoperable, and re-useable”.
- **The power of standardizing and sharing data**
- **A wide range of support and education**
- **Benefitting data science**
- **Creating applications to help the standards community**
- **Keeping up with innovation**

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MHRA draft guidance on randomised controlled trials generating real-world evidence to support regulatory decisions

- new guidance providing points to consider when planning a randomised clinical trial using real world data, with the intention of submitting this trial to gain a regulatory approval - such as extending the use of a medication into a new indication or a broader patient population.
- intended to be the first in a series of guidance documents addressing issues around using real-world evidence in support of a regulatory submission.
- considers aspects related to clinical trial authorisation, clinical trial design (including choice of endpoints and safety data requirements), and requirements in terms of database quality and inspection.
- current 6-week consultation

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Professional accreditation

- Royal Statistical Society
- CStat
- Grad Stat
- Data analyst

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Regulation- Risks

- Adds bureaucracy and red-tape
- Adds to costs of trials
- Substitutes rule-following for thinking
- ‘Independence’ can inhibit insight and communication
- Important studies disallowed for infringements that do not impact on validity of results
- Inhibits creativity

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Regulation- Benefits

- Sets standards
- Common understanding
- Ensures quality
- Important for training in a rapidly expanding field
- Aids transparency
- Builds trust