

Guidance on the drug-related content of clinical trial protocols



This guidance has been produced to help investigators with the pharmaceutical content of trial protocols.

The guidance is in 8 sections.

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Version control

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1. Trial procedures

1.1 Randomisation

Give details of the randomisation procedure. State who will receive new patient/randomisation alerts e.g. investigator/research nurse/pharmacy. State how they will be sent e.g. fax/email.

1.2 Code-breaks

If the trial is double-blinded give details of who holds the code-breaks and the procedure for unblinding. If an automated IVRS/IWRS system is used give details of who will have access to the unblinding facility e.g. investigator/pharmacy.

2. Treatment of patients

2.1 Introduction

Give general information about treatment i.e. patients will be randomised between <TREATMENT A> and <TREATMENT B>.

Example:

This is a randomised, multicentre, multinational phase III comparative trial. Eligible patients are randomised to one of two arms: <DRUG> or observation (standard of care).

2.2 Treatment schedule

Give details of drugs¹, doses (including maximum doses, number of doses), infusion times if applicable, routes of administration, frequency of cycle.

Give recommended scheduling of drugs if important i.e. paclitaxel before carboplatin, temozolomide 1 hour before radiotherapy.

For all drugs specify the method of dose rounding i.e. up, down, to the nearest dose or according to local policy.

Examples:

<DRUG> 130mg/m² iv infusion in 250/500ml 5% dextrose over 2 hours.

<DRUG> 300mg/m² orally tds days 1 to 5 (15 doses).

Days 1, 8 and 15 <DRUG> 425mg/m² sc injection.

Repeat every 3 weeks.

Vinblastine 6mg/m² (maximum 10mg) by slow iv bolus injection.

Temozolomide 200mg/m² orally daily for 5 days every 28 days.

2.3 Duration of treatment

Give details of the number of cycles / duration of treatment.

Examples:

Patients should receive <X> cycles of chemotherapy.

Treatment should be given continuously until disease progression or up to 2 years.

Treatment should continue for <X> cycles unless there is evidence of disease progression, unacceptable toxicity or at the patient's request.

Further cycles may be given at the discretion of the investigator.

¹ It is preferable to use generic names throughout, unless specific brand required. If specific brand specified state no substitution allowed.

2.4 Drug administration

Give information on the administration and on any special precautions that need to be taken when administering the drug.

For studies with oral drugs, give information on what to do if a patient misses a dose and information on what to do if a patient vomits a dose.

If applicable give information on how to deal with hypersensitivities. State if local policy can be followed.

Indicate if patient monitoring is required after drug administration.

If available, give information on specific treatments for extravasation. Reference can be made to the SPC or local policy.

Examples:

Patients will be instructed to take <DRUG> once daily preferably in the morning with up to 200ml of water at least one hour before or two hours after food. Patients should take the tablets at approximately the same time each day.

<DRUG> capsules will be taken on an empty stomach.

Missed doses will not be made up. The next dose must be taken as scheduled.

If a patient misses a dose, the dose should be taken later provided the patient remembers within 12 hours. If the patient does not remember within 12 hours, the missed dose should be omitted. Doses should NOT be doubled to make up for missed doses. [*Suitable for once a day dosing*]

If a patient vomits after taking the tablets, the dose should be replaced only if the vomited tablets can actually be seen and counted.

Observe the patient for one hour after administration of <DRUG>; blood pressure, pulse and temperature to be monitored every 15 minutes.

2.5 Dose modification

Give details of;

- Which tests e.g. FBC, U&E are required prior to each cycle of treatment and when they must be performed e.g. day 1 (or within 3 working days).
- Blood results etc required for treatment on cycle 1 day 1.
- Recommended dose reductions, interruption and permanent discontinuation for toxicities/adverse events. State whether dose escalation is allowed or not allowed.
- If the phrase 'when resolved' is used, define "resolved" e.g. to \leq grade 1, to baseline.
- Provide information on expected side-effects and the management of these. Reference can be made to the SPC.

2.6 Compliance (see also 3.7 Drug returns from patients)

Give any procedures for measuring patient compliance e.g. questionnaires, blood, urine or saliva tests, counting returned drugs etc.

Examples:

Patients should be asked to bring completed diary cards or other records and all their unused/remaining trial medicines (empty, open or unopened) with them to each clinic visit.

Patients will be instructed to keep a record of compliance with treatment, by means of using a "patient diary" that will be provided to them.

2.7 Support medication

Give details of support medication required, such as anti-emetics, pre-medication, hydration schedules, calcium folinate rescue, urine alkalinisation, mesna, G-CSF, antibiotics/antifungals, anti-diarrhoeals, thromboprophylaxis for central lines, drugs for tumour lysis, drugs for mouth care. State whether local practices can be used.

Examples:

Local anti-emetic policy may be followed.²

All patients should be pre-medicated with oral corticosteroids such as 8mg bd for 3 days starting 24 hours prior to <DRUG> administration.

A suggested hydration schedule for <DRUG> is given in table <X>, local practice may be followed.

All patients should receive prophylaxis against pneumocystis carinii pneumonia (PCP) with co-trimoxazole 960mg orally bd Monday/Wednesday/Friday. Patients who are allergic to co-trimoxazole should receive an alternative, such as nebulized pentamidine. PCP prophylaxis should continue throughout treatment and for at least 2 months after the last course of treatment.

Allopurinol 300mg/day orally is recommended for at least the first 28 days of therapy.

All blood products should be irradiated for patients in both arms of the trial.

The use of erythropoietin for the treatment of anaemia is not permitted.

The use of G-CSF is at the clinician's discretion.

2.8 Concomitant medication

All restrictions concerning concomitant medications, other treatments and conditions must be described. Include details of cautions and contra-indications where appropriate.

Examples:

Concomitant medication may be given as medically indicated. Details of the concomitant medication given must be recorded in the Case Report Form.

Radiotherapy may be given concomitantly for the control of bone pain or as indicated, however these irradiated lesions will not be evaluable for response.

The patients must not receive other anti-cancer therapy or investigational drugs whilst on study or within <X> days of starting or stopping treatment.

Systemic corticosteroids are not permitted except for the treatment of anaphylactic-like reactions.

2.9 Drug interactions / potential drug interactions

All known or potential clinically significant drug interactions (including drug–food interactions) must be indicated.

Examples:

There is a potential interaction between <DRUG> and warfarin. Patients have experienced elevated INRs and bleeding with this combination of drugs. Patients on warfarin and <DRUG> should have more frequent INR/PT determinations.

<DRUG> should NOT be taken with grapefruit or grapefruit juice.

² Please also give a suggested anti-emetic regimen as not all sites may be familiar with the drugs being used.

2.10 Actual versus ideal body weight

State whether actual or ideal body weight should be used in calculations. If ideal body weight is to be used give the formula. If applicable, include information on compensating for missing limbs/ascites.

Example:

The dose of <DRUG> will be calculated for each patient based on actual weight.

2.11 Calculating and recalculating BSA/doses

State method of calculating BSA e.g. Dubois and Dubois or refer to local policy.

State whether BSA/doses should be recalculated at each cycle or only under certain conditions. Give any conditions such as $\geq 10\%$ change and state what is compulsory and what is at clinician's discretion.

There is an increasing use of computer prescribing systems for chemotherapy. For sites using these systems it is usual practice to recalculate at each cycle. (Type in the new weight, press a button and the computer does all the hard work).

Example:

The patient's weight at baseline will be used to determine the dose of <DRUG> for the duration of the study. If a patient's weight changes by $\geq 10\%$ during the course of the study, the dose of <DRUG> should be recalculated. If a patient's weight changes by $< 10\%$ the dose may be adjusted according to local policy/clinician's discretion, but this is not an absolute requirement.

2.12 Carboplatin dosing

For carboplatin dosing using the Calvert formula; give the formula, the starting AUC and state which method of estimating GFR should be used (EDTA/DTPA, calculated creatinine clearance, measured creatinine clearance). If a calculated method is to be used, state which method of calculation e.g. Cockcroft and Gault, Wright and give the formula. If local policy may be followed state this.

If the AUC is dependent on the method of estimating GFR give the details e.g. if measured creatinine clearance use AUC5, if calculated creatinine clearance use AUC6.

State when to recalculate e.g. each cycle, if serum creatinine changes by $> 10\%$, according to local practice or must recalculate if $> 10\%$ change, optional if $\leq 10\%$ change.

Examples:

The GFR (and carboplatin dose) must be recalculated if the serum creatinine changes by $\geq 10\%$ from baseline. If there is a $< 10\%$ change recalculation is according to local policy.

The carboplatin dose will be determined using the Calvert formula (dose = (GFR + 25) x AUC) where GFR is estimated by a radioisotope method (EDTA/DTPA clearance). If the serum creatinine rises by $> 20\%$ from baseline, delay treatment and repeat isotope clearance scan. The serum creatinine value that triggered the re-scan becomes the new baseline value.

2.13 Dose capping

State whether dose capping is mandatory and specify the cap. If dose capping is not allowed or is at the clinician's discretion please indicate this.

Examples:

No doses are to be capped.

Dose capping is at the clinician's discretion.

Doses of all drugs will be capped at 2.2m².

The dose of <DRUG> will not be corrected for obese subjects.

If a patient weighs more than 1.15 x their IBW, use 1.15 x IBW to calculate body surface area.

The maximum body weight is 130kg [for mg/kg dosing].

The maximum dose of <DRUG> is 10mg.

2.14 Dose-banding

State whether or not dose-banding of drugs to $\pm 5\%$ is acceptable³. Indicate which drugs this applies to.

Please note, rounding the calculated dose to the nearest dose it is possible to give is not dose-banding. (e.g. if oxaliplatin 85mg/m² and BSA 1.79m²; calculated dose = 152.15mg, dose to give = 150mg; this is NOT dose-banding).

3. Trial drugs

3.1 Drug supplies

List all drugs used in the treatment arms including standard therapy.

Indicate if items such as filters, giving sets, infusion bags are provided.

For each drug indicate;

- Source of the supplies, (e.g. hospital own stock⁴, specific trial supplies free of charge, specific trial supplies at a discounted cost⁵).
- Formulation (e.g. tablet, capsule, solution for injection).
- Dose strength/concentration and size (e.g. 25mg and 100mg capsules, 10mg/ml in 50ml vial).
- Packaging of the supplies⁶ (e.g. 35 tablets per bottle, 6 vials per box). Include a sample label where appropriate.
- Whether or not the drug is an Investigational Medicinal Product (IMP) or a non Investigational Medicinal Product (NIMP⁷).

Examples:

<DRUG> will be supplied free of charge by <SUPPLIER>. <DRUG> is supplied in blister packs of 120 x 500mg film-coated tablets.

<DRUG> will be supplied free of charge to the local hospital pharmacies via a Central distribution company <NAME>. <DRUG> is supplied in vials of 100mg and 400mg of sterile liquid concentrate for solution for intravenous infusion. 100mg vials come in a box containing 6 vials. 400mg vials come in a box containing 1 vial.

³ An increasing number of centres are dose-banding chemotherapy. It may become routine practice in most sites and not allowing dose-banding could present problems for hospitals wishing to take part in trials.

⁴ If there is reimbursement of hospital stocks please state whether this is in money or free drug and give details of the reimbursement procedure.

⁵ Please avoid the 'buy-one-get-one-free' type of discounts, a '50% discount' is preferable.

⁶ All cytotoxic tablets/capsules should be provided in blister strips.

⁷ See EC Guidance on Investigational Medicinal Products (IMPs) and other medicinal products used in Clinical Trials.

<SUPPLIER> will provide commercially packaged stock for the hospital pharmacy at a 50% discount.

All chemotherapy and supportive medication is to be sourced and funded locally.

3.2 Drug ordering

For trial specific supplies indicate the supplier, how initial supplies are ordered or whether they are sent automatically and how subsequent supplies are ordered or whether they are sent automatically. If supplies are specific to an individual patient please specify. If supplies are sent when a patient is randomised, but may be used for any patient within the study please specify.

Examples:

Initial supplies of <DRUG> are sent out by <SUPPLIER> after they have been informed by <CO-ORDINATING CENTRE> that all approvals are in place. Subsequent supplies should be ordered by pharmacy using the form provided. Fax the completed form to <SUPPLIER> on <FAX NUMBER>.

The drug request form should be completed by the pharmacy for each patient randomised to receive <DRUG> and faxed directly to <SUPPLIER> on <FAX NUMBER>.

The <TRIALS OFFICE> will monitor stocks and reorder where required.

Supplies are patient specific and are automatically sent when a patient is randomised. If a patient is randomised before 12 noon drug will be dispatched the same day and should arrive the next working day. For patients randomised after 12 noon drug should arrive in two working days.

If a vial of <DRUG> is accidentally destroyed, i.e. by dropping the vial or through contamination, the pharmacist should contact <NAMED CONTACT> for replacement patient supplies.

3.3 Drug receipt

Specify any arrangements on receipt of supplies such as faxing an 'Acknowledgment of Receipt Form' or logging the receipt with an IVRS/IWRS system. Indicate what should be done if supplies are damaged on arrival.

Examples:

Return the completed original delivery note to <SUPPLIER> in the prepaid envelope provided. A copy should be kept in the Pharmacy File.

Complete details on Acknowledgement of Receipt Form and fax back to <NAME> on <FAX NUMBER>.

Acknowledge receipt of supplies on the IVRS system.

If supplies are damaged on arrival contact the trials office. Damaged supplies should be destroyed on site and a drug destruction form completed.

Stop any temperature monitoring devices and return any 'out of range' devices or download the temperature record and email to <CO-ORDINATING CENTRE>.

3.4 Drug storage

For all drugs specify the storage conditions and the shelf life of the unopened product.

Examples:

Unopened vials of <DRUG> may be stored at controlled room temperature 25°C; excursions permitted from 15°C to 30°C. It should be retained in the original package to protect from light.

Store between 2-8°C. Do not freeze. Unopened containers have a shelf life of 2 years.

Store between -15 and -25°C. The vials should not be shaken. Unopened vials have a shelf life of 3 years.

Store below -70°C.

Stability studies indicate that this formulation is stable for <Y MONTHS> at <X°C>.

3.5 Drug dispensing

State the procedure and amounts to be given each time. Describe the dosage form, packaging and labelling of IMP and additional arrangements for labelling blinded drug supplies.

For drugs requiring reconstitution give the following information⁸

- The method of reconstitution of the investigational product.
- Details of;
 - The diluent (i.e. WFI, 0.9% sodium chloride) and the container (i.e. infusion bag, bottle) to be used.
 - Concentration of infusions.
 - Compatibility of the investigational product with other drugs and/or infusion equipment, if applicable.
 - Any special precautions to be taken when reconstituting (i.e. use of filters, protection from light).
 - The stability and storage of the reconstituted product.

Examples:

Calculate the volume of <DRUG> 10mg/ml solution required for the dose. Draw up the calculated volume of <DRUG> from the 50ml and 10ml vials provided taking care not to cause foaming. Slowly add this volume to the infusion bag containing 0.9% sodium chloride or 5% dextrose injection to give a final concentration of 1 to 4mg/ml. To mix the solution, gently invert the bag in order to avoid foaming. Do not shake the bag.

No incompatibilities between <DRUG> and polyvinyl chloride or polyolefin bags or infusion sets have been observed.

Prepared infusion solutions should be used immediately. If necessary prepared solutions may be stored in a refrigerator (2-8°C) and are physically and chemically stable for up to 24 hours.

The lyophilized powder is reconstituted by adding 10ml of Water for Injection. Do not administer the reconstituted solution without further dilution. The reconstituted solution must be further diluted in an infusion of 250 to 500ml dextrose 5%.

Solutions should be stored in non-PVC bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets.

Solutions are stable for 24 hours at 25°C.

Please be aware that mixing two or more IMPs together constitutes a manufacturing process unless indicated as part of the product licence. Manufacturing can only be performed in a pharmacy with an IMP licence. Examples of products that are required to be made in an IMP

⁸ For licensed drugs these details can be found in the SPC. It is acceptable to state "refer to SPC" for licensed drugs in common use.

licensed facility include, doxorubicin and vincristine mixed together in infusion pumps, doxorubicin and X-ray contrast agents mixed together for hepatic artery administration and melphalan and actinomycin mixed together for isolated limb perfusion techniques. Many hospital pharmacies do not have an IMP licence and it is worth investigating whether this will be a problem before the protocol is written.

3.6 Drug accountability

Give details of documentation required and for which drugs. For drug accountability/dispensing logs, state whether they are patient specific or batch specific etc. State any requirements such as faxing/sending copies to the trial co-ordinating centre on completion. List documentation provided and state whether hospitals are allowed to use their own documentation if preferred. If end-of-study drug reconciliation is required, please state this. Appropriate forms should be provided.

Clearly distinguish between a) 'full drug accountability' and b) 'drug accountability/traceability'

a) 'full drug accountability' i.e. accounting for all IMP provided to a site. (What has come in to a site, what has gone out to which patients, what has been destroyed/returned to sponsor, what is left on the shelf). In the event of a drug recall can all patients who received any of the affected batch be identified. This requires drug accountability/dispensing logs;

b) 'drug accountability/traceability' e.g. for IMP/NIMP from hospital stocks. (What has gone out to which patients). In the event of a drug recall can all patients who received any of the affected batch be identified. This information could be captured on pharmacy aseptic unit worksheets or drug accountability/dispensing logs.

Examples:

Full drug accountability records must be maintained for <DRUG X> and <DRUG Y>. Use the Drug Dispensing Logs provided. Hospitals may amend the Drug Dispensing Logs provided or use their own documentation if it captures all the information requested on the Drug Dispensing Logs.

For <DRUG R>, <DRUG S> and <DRUG T> records must detail; patients name/identifier, date and quantity dispensed, batch number of drug. It is expected that pharmacy aseptic unit worksheets will be sufficient.

The drug dispensing and inventory logs should be kept up to date and have to contain the following information; patient identifier, date and quantity received at site, date and quantity dispensed, date and quantity returned/destroyed at site.

The inventory must be available for inspection by the monitor at every monitoring visit.

At the conclusion of the study the overall numbers of drug shipped to the centre, the number dispensed and the number destroyed or returned will be provided by the pharmacy. An account must be given of any discrepancy.

3.7 Drug returns from patients (see also 2.6 Compliance)

State which drug(s)⁹ if any are expected to be returned from the patient to the hospital/site/pharmacy.

State what is required to be done with the returns (and by whom); count and record in the CRF or in the pharmacy documentation, save the returns until verified by a monitor or dispose of as convenient, return to the sponsor/supplier or destroy on site.

⁹ For health and safety reasons used and partially used vials of cytotoxics/monoclonal antibodies are not kept (and neither are the outer boxes).

Examples:

There is no requirement to collect patient returns.

The Research Nurse will count patient returns and record in the patient's CRF. The returns can then be disposed of according to local policy.

Patient returns of <DRUG> should be returned to pharmacy for counting and recording in the patient's Dispensing Log. Returns may then be destroyed on site according to local practice (verification by monitor not required).

Patients will be requested to return medication to the pharmacy. Returns will be counted and recorded in the pharmacy documentation. Patient returns should be kept until verified by the study monitor and then returned to <SPONSOR>. The monitor will arranged transport.

3.8 Drug disposal

Give details of the disposal of used drug, partially used drug, drug left unused at the end of the study and expired drug. Disposal may be by either returning drugs to the sponsor/supplier or by disposal at site. Disposal of patient returns if applicable could be mentioned here as well as in Section 3.7 'Drug returns from patients'.

If the co-ordinating centre would like a copy of any certificates of disposal, state this and how to send the copy (fax, post). If the co-ordinating centre would like to give authorisation before any disposal please state this.

Used / partially used vials ¹⁰	Disposal at site according to local hospital policy.
Drug left unused / expired drug	Return to sponsor.
Drug left unused / expired drug	Disposal at site according to local hospital policy. A dated certificate of disposal should be completed and retained in the Pharmacy File.
Drug left unused	At the end of the study, once authorised to do so, any unused drug should be disposal of at site according to local hospital policy. A dated certificate of disposal should be completed. The original should be placed in the Pharmacy File and a copy faxed to the Trials Unit.
Patient returns	Return to sponsor.
Patient returns	Disposal at site according to local hospital policy.

¹⁰ Used/partially used vials are accounted for in drug accountability logs and therefore do not need their disposal accounted for separately (nor certificates of disposal) as it is inherent in the 'use' of the vials.

4. Glossary of formulae

Formulae for; body surface area (BSA), creatinine clearance, carboplatin dose, ideal body weight (IBW).

Formula for BSA

DuBois and DuBois formula

$$\text{BSA [m}^2\text{]} = \text{weight [kg]}^{0.425} \times \text{height [cm]}^{0.725} \times 0.007184$$

Formulae for creatinine clearance

Cockcroft and Gault formula

$$\text{Men: CrCl [ml/min]} = \frac{(140 - \text{age}) \times \text{weight [kg]} \times 1.23}{\text{SeCr [\mu mol/l]}}$$

$$\text{Women: CrCl [ml/min]} = \frac{(140 - \text{age}) \times \text{weight [kg]} \times 1.04}{\text{SeCr [\mu mol/l]}}$$

Schwartz formula

$$\text{CrCl [ml/min/1.73m}^2\text{]} = \frac{F \times \text{height [cm]} \times 88.4}{\text{SeCr [\mu mol/l]}}$$

Infants (< 1 year of age)	F = 0.45
Male, 1-16 years	F = 0.55
Female, 1-21 years	F = 0.55
Male, 16-21 years	F = 0.70

Wright formula

Jaffe Serum Creatinine without CK:

$$\text{GFR} = \frac{(6580 - (38.8 \times \text{age})) \times \text{BSA} \times (1 - (0.168 \times \text{sex}))}{\text{SeCr [\mu mol/l]}}$$

sex: female = 1, male = 0

Enzymatic Serum Creatinine without CK:

$$\text{GFR} = \frac{(6230 - (32.8 \times \text{age})) \times \text{BSA} \times (1 - (0.23 \times \text{sex}))}{\text{SeCr [\mu mol/l]}}$$

sex: female = 1, male = 0

Formula for carboplatin dose

Calvert formula

$$\text{Carboplatin dose [mg]} = (\text{GFR} + 25) \times \text{AUC}$$

Formulae for IBW

Devine formula

$$\text{Men: IBW [kg]} = 50\text{kg} + 2.3\text{kg per inch over 5 feet}$$
$$\text{Women: IBW [kg]} = 45.5\text{kg} + 2.3\text{kg per inch over 5 feet}$$

Lorenz formula

$$\text{Men: IBW [kg]} = (\text{height [cm]} \times 0.75) - 62.5$$
$$\text{Women: IBW [kg]} = (\text{height [cm]} \times 0.5) - 25$$

5. Suggested capecitabine dose banding table

Exact dose (mg)	Banded dose (mg)	Number of tablets	
		500mg	150mg
475 – 549	500	1	0
550 – 624	600	0	4
625 – 699	650	1	1
700 – 774	750	0	5
775 – 849	800	1	2
850 – 924	900	0	6
925 – 974	950	1	3
975 – 1049	1000	2	0
1050 – 1124	1100	1	4
1125 – 1224	1150	2	1
1225 – 1374	1300	2	2
1375 – 1474	1450	2	3
1475 – 1574	1500	3	0
1575 – 1724	1650	3	1
1725 – 1899	1800	3	2
1900 – 2074	2000	4	0
2075 – 2224	2150	4	1
2225 – 2399	2300	4	2
2400 – 2574	2500	5	0
2575 – 2724	2650	5	1
2725 – 2899	2800	5	2
2900 – 3074	3000	6	0

6. Manipulation of IMPs in the pharmacy

- As the programme of MHRA GCP inspections under EC regulations has been rolled out a number of issues about the supply of Investigational Medicinal Products (IMPs) from hospital pharmacies has emerged.
- The key issue is that if the IMPs are considered under the regulations to be manufactured rather than dispensed, preparation can legally take place in the pharmacy only under a Manufacturing Authorisation for IMPs (MAIMP) which requires the licence holder to name a trial-specific Qualified Person (QP). Most hospital pharmacies do not have access to the services of a QP.
- Preparation of an individual dose of an IMP, such as dissolving a sterile powder and adding the resulting solution to an infusion bag is not classed as manufacturing and can be carried out in any suitably equipped hospital pharmacy under the exemption detailed in Regulation 37 of The Medicines for Human Use (Clinical Trials) Regulations 2004.
- Mixing two therapeutically active drugs together in an infusion bag, or crushing tablets to make a suspension, however, is classed as manufacturing and is not allowed without an MAIMP and nominated QP.
- Care should be taken to use only those medicinal products specifically identified in the CTA application. If, for example, a drug is available from more than one manufacturer, and the application identifies a particular brand (e.g. Taxol®), all trial centres will be required to use that brand only to treat patients in that study. If the application identifies the drug in its generic name (e.g. paclitaxel) trial centres will be able to use which ever brand of drug is standard at their sites. It is preferable to describe drugs by their generic name and not by brand.
- If trusts source named-patient doses of IMPs from a third party under a service agreement, the supplier must hold an MAIMP.
- To avoid the risk of later confusion when interpreting the application to a study of The Medicines for Human Use (Clinical Trials) Regulations 2004, the CTA application and the trial protocol must state clearly which medicines are and which are not intended to be classified by the CTA as IMPs for the purposes of the study.
- ***Although compliance with these rules presents a considerable challenge, several trusts have been severely criticised when found by the MHRA not to have complied. Compliance in future studies is therefore essential.***
- When planning new studies, ***authors are very strongly recommended to discuss dispensing of IMPs with their trust's Chief Pharmacist at the earliest possible stage of protocol development,*** before submission of the CTA application.

7. Labelling of Investigational Medicinal Products (IMPs)

Manufacturers' packs of Investigational Medicinal Products (IMPs) should be labelled in accordance with the principles and detailed guidelines of Good Manufacturing Practice for Medicinal Products (The Rules Governing Medicinal Products in The European Community, Volume IV). Other relevant EU guidelines should also be taken into account at the appropriate stages of drug development.

Pharmacy departments routinely review the suitability of IMP labelling to ensure that clinical trial & patient identification is included and that risk management and local policy requirements are followed. Dispensed IMPs should be labelled to the same standards as all other dispensed medicines. This usually results in the pharmacy department generating additional labels to be attached to the IMP without obscuring the original labelling.

Additional labelling requirements may include:

- Principal Investigator: name and contact number
- Hospital / Pharmacy address and contact details
- Patient Identification: Patients Name / Initials
- Date of Dispensing
- Visit / Cycle Number
- Comprehensive dosing instructions (unless included in manufacturer's label)
- Cautionary and advisory labels e.g. with or after food
- Batch Number / Expiry Date (this will not be on the package if medication is transferred to another container).
- 'For Clinical Trial Use Only'
- 'Keep Out of Reach of Children'
- Storage requirements
- 'Please return unused medication to the hospital pharmacy'
- 'Cytotoxic Handle with Care'
- 'Not to be handled by pregnant women'
- 'This is container x of y containers'

Additional labels are usually added to correct omissions from manufacturers' IMP labels. Common omissions are listed below.

- Information omitted.
- Information unclear – Directions for use are not clear for the patient i.e. 'as directed'.
- Storage requirements – Not clearly indicated.
- Risk Management – The information maybe contained in the patient information leaflet or trial card however the patient may lose this information. Also this information may not necessarily be available to carers or general medical staff.
- Multi-lingual booklets/labels – It is difficult for the patient to find the UK information.

EU GMP Volume 4, Annex 13 clearly states the requirements for labelling IMPs and details the information required on the immediate container and outer packaging; in the general case, in the case when the immediate container takes the form of blister packs or small packaging units and in the case when the immediate container and the outer packaging are intended to remain together.

Pharmacy departments can provide advice on the labelling of IMPs. Liaising with pharmacy clinical trials staff during the early stages of trial set-up may prevent the need for additional labels.

A good example of the content of a standard IMP label is shown below:

For Clinical Trial Use Only		
Protocol Number: XXXXXXXX	XXXXXXXX Trial	
Principal Investigator: XXXXXXXX	Tel: XXXXXXXX	Site: XXXXXX
IMP Name, Strength & Formulation / Placebo (if applicable)		
Directions for use: Clearly stating the dose, frequency, administration requirements and duration of therapy.		
Cautionary and advisory labels e.g. with or after food.		
Patient No: XXXXXXXX	Patient Name: XXXXXXXXXXXXXXXX	
Visit No: XXXXXX	Date of Dispensing: XXXXXXXX	
Quantity: XXXXXX	Storage: XXXXXXXXXXXXXXXXXXXX	
Batch Number: XXXXXXXX	Expiry Date: XXXXXXXX	
Please return any unused medication at your next visit.		
Sponsor/CRO/Investigator Contact Information		
Keep Out of the Sight and Reach of Children		

8. Oral anti-cancer therapy

Between November 2003 and July 2007 the National Patient Safety Agency (NPSA) received reports of three deaths and a further 400 patient safety incidents concerning oral anti-cancer medicines. In response to this the NPSA issued advice to the NHS about safe practice with oral chemotherapy in January 2008 (Rapid Response Report – NPSA/2008/RRR001).

When drafting protocols and planning studies involving oral chemotherapy in any arm of a study, authors must ensure that the following objectives are addressed:

- Patients should be fully informed and receive verbal and up-to-date written information about their oral anticancer therapy from the initiating hospital.
- This information should include contact details for specialist advice, which can be shared with non-specialist practitioners.
- Written information, including details of the intended oral anti-cancer regimen, treatment plan and arrangements for monitoring, taken from the original protocol should be given to the patient.