Mock examples to assist with the question 'Is it a clinical trial of an investigational medicinal product?'

Researchers should consult the available algorithm to help answer the question. The following examples are categorised in the same order as the algorithm, i.e. starting with 'Is it a medicinal product?' and ending with 'How are you looking for those effects?'.

The examples are not exhaustive but aim to cover key examples that have been previously asked of MHRA CTU.

The examples do not provide guidance on whether a medicinal product as used in a CTIMP is an investigational medicinal product (IMP) or a non-IMP. Guidance on this topic is available here: https://ec.europa.eu/health/sites/default/files/files/eudralex/vol-10/imp_03-2011.pdf

The examples also do not provide guidance on whether a CTIMP is a type A, B or C trial. Guidance on this topic is available here: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/343677/Risk-adapted_approaches_to_the_management_of_clinical_trials_of_investigational_medicinal_products.pdf

A – Is it a medicinal product?

If you answer no to all the questions in column A, the activity is not a clinical trial on an IMP. If you answer yes to any of the questions below go to column B.

A.1 Is it a substance or combination of substances presented as having properties for treating or preventing disease in human beings? Note: a substance is any matter irrespective of origin e.g. human, animal, vegetable or chemical that is being administered to a human being.

CTIMP	Not CTIMP
Treating an acute exacerbation of COPD with Chinese herbal medicine in addition to antibiotic use. An RCT, placebo controlled study evaluating safety and efficacy of the herbal medication. Herbals can function as medicines if presented as treating a disease state.	Targeted molecular imaging of CA125 in high grade serous ovarian cancer using ^{89}Zr-tracer positron emission tomography (PET) magnetic resonance imaging (MRI). The aim was to equate imaging with serum marker levels as a marker of disease. In future this could be used to diagnose recurrent disease so future studies may be CTIMPs.
Treatment of Otitis Externa with Topical Leucillin. Leucillin is an antiseptic spray for animals but the study proposes it as having antibacterial properties for treating a specific disease. Therefore it is considered a medicine.	

A.2 Does the substance function as a medicine? i.e. can it be administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a

pharmacological, immunological or metabolic action or to making a medical diagnosis or is otherwise administered for a medicinal purpose?

CTIMP	Not CTIMP
A comparison of ^{99M}Tc with ICG fluorescence sensitivity for sentinel node localisation. The aim was to establish ICG as non-inferior detection in breast cancer, which makes it a diagnostic agent in the study, thus a medicine.	Aromatherapy – There are no identified pharmacological properties and therefore studies of aromatherapy are not CTIMPs.
An RCT of the efficacy of an oral probiotic on motor symptoms in Parkinsons disease. The probiotic is proposed as having a physiological mechanism with a scientific rationale for use in Parkinsons. Despite the probiotic usually being a food supplement, in this study it is presented as a medicine, and the outcomes were clinical.	Evaluating Colgate toothpaste effects on the oral microbiome in patients with gingivitis. The objective was to evaluate commensal prevalence. Toothpaste is not usually a medicine and the proposal was not clinical. However, a full mechanism was proposed and future studies may be CTIMPs if the toothpaste is proposed as treating gingivitis.
	Protein powder used as a dietary supplement in elderly subjects known to have poor nutritional intake. The study is evaluating the effects on muscle function (hand grip strength). This is accepted as a food with no function as a medicine.
	A study to evaluate the effects of a 20ml bottle of probiotic once a day on stress from university examinations. No physiological mechanism was proposed and there was no disease state being evaluated.

A.3 Is it an active substance in a pharmaceutical form?

CTIMP	Not CTIMP
Pharmaceutical form includes tablet, capsule, solution for injection, topical gel/cream, sachet, oral solution with an identified strength, skin patch etc. An active substance is one presented as having a mechanism that involves biological activity.	Broccoli capsule orally for 12 weeks in patients with asthma to test the effects on inflammatory biomarkers. It was clarified in the protocol that the broccoli was in a capsule form in order to be concentrated and prevent patients having to ingest a disproportionate volume of raw vegetable per day.
Vehicle controlled double blinded, randomised study of a bacterial blend to modulate the gut in adults with mild to moderate plaque psoriasis. The food grade bacteria were in a 3g sachet containing 10^8-10^9 c.f.u per sachet, to be given once daily for 26 weeks. The outcomes were clinical scores of disease severity.	

B – Is it *not* a medicinal product?

If you answer yes to the question below in column B the activity is not a clinical trial on an IMP. If you answer no to this question below go to column C.

B.1 Are you only administering any of the following substances?

- Human whole blood - This does not include derivatives of human whole blood, human blood cells and human plasma that involve a manufacturing process

CTIMP	Not CTIMP
	To evaluate overall survival of patients with high-risk AML, ALL or MDS after partially matched unrelated or haploidentical donor stem cell transplantation. The stem cells were completely unmanipulated and are therefore not considered as a medicinal product.

- Human blood cells

CTIMP	Not CTIMP

- Human plasma

CTIMP	Not CTIMP
Platelet rich plasma (PRP) where the process involves mixing the PRP with activators, such as ascorbic acid and thrombin, to produce a gel. This is considered as manipulation and therefore the resulting product is a medicine. The gel is proposed as having a pharmacological action and is used to treat diabetic foot ulcers.	Autologous platelet rich plasma, collected, processed and administered all within a single surgical procedure with no other substances used for activation or manipulation and used in a dental procedure.
Unmanipulated PRP vs steroid in a study evaluating efficacy in impingement syndrome of the shoulder. Although the PRP is not a medicine the study is evaluating steroid as a comparator, and as that is a medicine the study has to be a CTIMP (providing criteria in columns C, D and E are also met).	Autologous blood drawn into an anticoagulant (such as sodium citrate or EDTA), centrifuged and buffered to achieve physiological pH (for example with bicarbonate), resulting in platelet rich plasma. The anticoagulant and buffering are not manipulating the platelets and so the product is not considered a medicine.
Platelet rich growth factors used in dentistry that are subject to additional manipulation, including addition of calcium chloride, fall within the definition of a medicinal product whereas a product that has not been subject to these additional manipulation steps falls outside the definition of a medicinal product. If in doubt then contact the MHRA Borderline team.	

- Tissues except a somatic cell therapy medicinal product - Somatic cell therapy medicinal products use somatic living cells of human (or animal) origin, the biological characteristics of which have been substantially altered as a result of their manipulation to obtain a therapeutic, diagnostic or preventative effect (in humans) through metabolic, pharmacological and immunological means.

CTIMP	Not CTIMP

- A food product (including dietary supplements) not presented as a medicine - Any ingested product which is not a medicine is regarded as a food. A food is unlikely to be classified as a medicine unless it contains one or more ingredients generally regarded as medicinal and indicative of a medicinal purpose.

CTIMP	Not CTIMP
A blended bacterial formulation in a 3g sachet to be given orally. The product is usually a food supplement. The study is a double blind RCT evaluating its effects on clinical outcomes in psoriasis. In the study the product is presented as having medicinal properties (as per column 'A' in the algorithm) and to treat a disease, therefore it is no longer considered a food in this setting.	The effects of dietary nitrate supplementation on pregnancies complicated by chronic and new onset hypertension. A specified volume of beetroot juice was to provide the nitrate. Whilst there were clinical outcomes, beetroot juice was not presented as having medicinal properties and so was a food.
	Almonds and their impact on immune optimization to viral infection: a randomised controlled trial of vaccination model of immune response. The almonds were not in any pharmaceutical form so are a food.
	A study to investigate freeze-dried dragon-fruit effects in lowering blood pressure in healthy volunteers. Whilst the outcomes are clinical the presentation of the product was as a food, with no medicinal properties.

- A cosmetic product - A "cosmetic product "means any substance or preparation intended for placing in contact with the various external parts of the human body (epidermis, hair system, nails, lips and external genital organs) or with the teeth and mucous membranes of the oral cavity with the view exclusively or principally to cleaning them, perfuming them or protecting them in order to keep them in good condition, change their appearance or correct body odours.

CTIMP	Not CTIMP
An RCT to evaluate the efficacy of cysteamine cream compared to hydroquinone in the treatment of melasma. The cysteamine was presented as having a pharmacological action through inhibiting melanogenesis in an underlying disease state, which changes it from a cosmetic to a medicine.	Evaluation of skin lightening and tolerability of cysteamine cream in individuals with skin hyperpigmentation. Cysteamine is presented as having a depigmentation action but is not treating an underlying disease state.

- A medical device

CTIMP	Not CTIMP
An intracardiac device used with a separate antithrombotic regimen of an anticoagulant and an antithrombotic. The study is evaluating withdrawal of the antiplatelet drug. Withdrawal of a drug is considered as evaluating efficacy and the study is assessing the drug component not the device.	A radio-enhancer given with radiotherapy vs radiotherapy alone, with chemotherapy, to treat a specified carcinoma. The radio-enhancer is not a medicine, and neither is radiotherapy. Chemotherapy is not under specific evaluation and is background therapy in all patients. Therefore there is no IMP.

C – What effects of the medicine are you looking for?

If you answer no to all the questions in column C the activity is not a clinical trial of an IMP under the scope of Directive 2001/20/EC. If you answer yes to any of the questions below go to column D.

C.1 To discover or verify/compare its clinical effects?

CTIMP	Not CTIMP
^{18}F fluciclovine PET imaging in glioma. The objective was to use PET to distinguish between low and high grade tumours, which is a clinical outcome.	Routine versus selective use of drug x in STEMI patients treated by primary percutaneous coronary intervention. The primary outcome is LVEF and other clinical outcomes are included in the study. This is not a CTIMP however as the objective is the strategy of the timing of treatment, not specifically evaluating the efficacy of the drug.
	Randomised controlled trial of local anaesthesia vs PCA for control of post-operative pain. The primary outcome is pain VAS. This is the strategy of the route of pain control rather than the evaluation specifically of the medicines involved.
	Evaluation of antibiotics alone vs surgery plus antibiotics to treat appendicitis in children. The objective was to assess the value of surgery or no surgery, and all children received antibiotics. Therefore the trial is not directly investigating the clinical effects of antibiotics, surgery is not medicinal and so the proposal is not a CTIMP.

C.2 To discover or verify/compare its pharmacological effects, e.g. pharmacodynamics?

CTIMP	Not CTIMP
A double blind RCT to compare the PD profile of disport, botox and xeomin in the extensor digitorum brevis model in healthy adults. The objective was to demonstrate a longer duration	An RCT of an angiotensin receptor blocker in aortic stenosis, where losartan is specified as the ARB to be used. The primary outcome measure is aortic valve calcification and other

of action of disport, which is a pharmacodynamic outcome.	clinical parameters. This was presented as studying the angiotensin pathway and therefore is evaluating losartan as a probe of that pathway rather than evaluating the drug itself. Any other ARB could have been used to meet the study outcomes.
	Evaluating the action of a novel 5-HT3 receptor partial agonist on visceral sensation, small bowel and colonic function in health volunteers. This early study was evaluating the physiology of the gut only, but future studies may be a CTIMP if they are evaluating the mechanism of a new active substance for treatment of GI disease.

C.3 To identify or verify/compare its adverse reactions?

CTIMP	Not CTIMP
Targeted metabolic modulation of the right ventricle and pulmonary circulation in pulmonary arterial hypertension using exenatide. Outcomes were cardiac endpoints and safety (specifically glucose effects). Safety was a specific study objective.	A study evaluating intravenous iron infusions given as standard of care and the effects on physiological levels of phosphate. Safety was also being recorded but not as a specific objective. Safety monitoring is expected in any study of a medicinal product but if it is only to ensure safe conduct, not as a specific objective, that is not sufficient alone to consider a study as a CTIMP.
An open label exploratory study to assess the feasibility of using methotrexate as a standard treatment for women with unruptured tubal ectopic pregnancies. The outcomes were not only feasibility but safety in this indication was explicitly an objective.	

C.4 To study or verify/compare its absorption, distribution, metabolism or excretion?

CTIMP	Not CTIMP

D – Why are you looking for those effects?

If you answer no to all the questions in column D the activity is not a clinical trial of an IMP under the scope of Directive 2001/20/EC. If you answer yes to any of the questions below go to column E.

D.1 To ascertain or verify/compare the efficacy of the medicine? Efficacy is the concept of demonstrating scientifically whether and to what extent a medicine is capable of diagnosing, preventing or treating a disease and derives from EU pharmaceutical legislation.

CTIMP	Not CTIMP
An unlicensed treatment for diabetic foot ulcer being used on a compassionate basis, with a	A consumer study to only evaluate taste and mouth feel of nicotine replacement products.

clear protocol, n=10, specific eligibility. 'Compassionate use' in the UK falls within Guidance note 14 and is for an individual subject. The proposal is not a case series but rather is a small pilot trial.	Taste is not considered a clinical or efficacy endpoint.
A double blind, randomised, placebo controlled evaluation of a medicine to treat cancer with some objectives for feasibility and others to assess early efficacy. This is a pilot CTIMP as not all objectives are feasibility.	Randomised, single blind, crossover study to evaluate taste attributes and acceptability of an oral unlicensed medicine, using a spray-and-expel method
Impact of alemtuzumab exposure on risk of infection and GVHD in children undergoing stem cell transplant. The key objective was evaluating PK and correlating exposure with efficacy and safety.	Double blind, randomised study of intensive treatment for orthostatic hypotension in the elderly vs standard of care. *All* outcomes have been stated as feasibility to inform on a larger multisite trial in the future.
A study of high dose vitamin D given to subjects who are not deficient to evaluate effect on the incidence of acute respiratory tract infection. The vitamin D is not restoring a deficiency but is being used to provide supra-physiological levels to treat a disease.	A study to evaluate vitamin D in vitamin D deficient subjects and the effect on rhinovirus symptoms. The aim was clarified as not using vitamin D to treat rhinovirus, rather it is restoring levels in subjects clearly identified as deficient (through eligibility criteria) and thus restoring a normal physiological response to rhinovirus.

D.2 To ascertain or verify/compare the safety of the medicine?

CTIMP	Not CTIMP

E – How are you looking for those effects?

If you answer yes to <u>all</u> these questions the activity is a non-interventional trial (not a CTIMP) which is outside the scope of Directive 2001/20/EC. If your answers in columns A,B,C & D brought you to column E and you answer no to any of these questions the activity is a clinical trial of an IMP within the scope of the Directive.

E.1 Is this a study of one or more medicinal products, which have a marketing authorisation in the Member State concerned?

CTIMP	Not CTIMP
A post-authorisation safety study to evaluate the effect of drug x on serum potassium levels in the licensed indication. The dosing decision is made as part of the trial and the key objective is based on a safety parameter that was identified as a potential risk during development. Just because its licensed, being used in the study within the licensed indication and evaluating a known risk doesn't mean it is automatically not a CTIMP.	A post-authorisation safety study to assess the overall safety profile of drug x within its indication. The study is open label, patients are already on the drug, there are no additional interventions above standard of care and statistics are all descriptive.

E.2 Are the products prescribed in the usual manner in accordance with the terms of that authorisation?

CTIMP	Not CTIMP
A study to assess the role of adrenaline in injectate solution during endoscopic resection of colorectal polyps. Adrenaline has a marketing authorisation but in the study was being used at a different dose and in an indication not included in any SmPC.	
Gentamicin given via the intravesical route for treatment of recurrent UTI. Whilst gentamicin is licensed, this is a new route of administration. It is a route allowed in clinical practice/hospital guidelines but this is not covered in the license so is a CTIMP.	

E.3 Does the assignment of any patient involved in the study to a particular therapeutic strategy fall within current practice and is not decided in advance by a clinical trial protocol? - Assignment of patients to a treatment group by randomisation planned by a clinical trial protocol cannot be considered as current practice

CTIMP	Not CTIMP
A comparison of local anaesthetic via rectus sheath block to saline placebo for pain control. This is not comparing techniques of pain control but is randomising patients to an active or placebo, so treatment is determined only by the protocol, therefore the proposed study is a CTIMP.	
Randomised controlled trial of surfactant versus expectant management of preterm babies with respiratory distress. Both arms are considered as standard of care, depending on the specific hospital guidelines and clinical status, but the study randomises treatment, therefore it is a CTIMP.	
Comparison of 3 fluids for maintaining euvolaemia in the peri-operative period in neurosurgery. The fluids are all used interchangeably within standard practice, the key outcome was hyperchloraemia (which is a safety outcome) but assignment is via block randomisation.	

E.4 Is the decision to prescribe a particular medicinal product clearly separated from the decision to include the patient in the study?

CTIMP	Not CTIMP

	Safety of chemotherapy in patients with recurrent glioblastoma. Whilst safety was being evaluated there was no randomisation, all monitoring was as per standard of care and at usual timepoints and prior to study entry all patients had already started chemotherapy.

E.5 Will no diagnostic or monitoring procedures be applied to the patients included in the study, other than those which are applied in the course of current practice?

CTIMP	Not CTIMP
A newly licensed combination product to be prescribed per local practice but additional measures were included that were outside standard of care and the objectives/endpoints related to efficacy evaluations. The additional endpoint measurements beyond standard of care make it an interventional study.	

E.6 Will epidemiological methods be used for the analysis of the data arising from the study?

CTIMP	Not CTIMP
	A study of clinical outcomes of inhibitor-positive patients with haemophilia A already receiving immune tolerance induction therapy with no additional interventions above standard of care. All analyses are descriptive, using frequency distributions and descriptive statistics.