"want for clinical trials. "a clinical trial

“ Want to volunteer fora clinical trial and get paid?” This was the unexpected advertisement whichappeared on my Twitter feed and triggered my curiosity for clinical trials.

“ Aclinical trial is any research study that prospectively assigns humanparticipants or groups of humans to one or more health-related interventions toevaluate the effects on health outcomes.” 1. In a matter of clicks and a completion of one short form you can beconsidered to take part in a clinical trial. I wondered why someone would puttheir life at risk for money, especially in light of the clinical trialinvolving the drug TGN1412 that went horribly wrong.

However, to my surprisethere are many willing individuals around the world participating in clinicaltrials. According to ClinicalTrials. gov, currently there are 246, 719 clinicalstudies with locations in all 50 States and in 201 countries. Experimenting andtesting have long been a part of medicine and these clinical trials are a keyresearch tool for advancing medical knowledge and patient care. They can detectand reduce the risk of disease. However, despite the widespread use of clinicaltrials and their integral part in medical research, there exist moral issuessurrounding this type of experimentation. Risks from participation may notbalance with the clinical benefit; some trials may not lead to any significantresults or conclusions, but the participants could be harmed in the process.

There have been many cases where trials havebeen unsuccessful and have negatively impacted patients, sometimes leading tomortalities. I explore the causes forthe failure of one particular trial, the TGN1412 case and cover

other examplesof recent failed trials as a result of ethics, bad process and scientificfactors. I also explore other general ethical issues and recommendations duringthe conduct of clinical trials.

The findings will allow me to evaluate andsummarise the lessons learned. I will demonstrate that many of these examples of bad process could havebeen avoided if those who conducted the trials followed the Declaration of Helsinki, which is a list of ethical codes regardinghuman experimentation developed for the medical community. The term ‘ human experimentation’ can still remind manyof the infamous experiments conducted on war prisoners during World War II. Theunethical handling of human subjects in medical research was also carried on inthe post-war period. The trials targeted vulnerable populations such as the mentally-ill, disabled, the poor and ethnic minorities. A prime example was the Tuskegeesyphilis study, which aimed to observe the natural progression of untreatedsyphilis in rural African-American men in Alabama under the appearance ofreceiving free health care from the United States government2. However, following these cases many ethical guidelines and regulations were putin place, including the Declaration of Helsinki, which I have mentioned above. Despite the introduction of these, there are still areas where clinical trialscould be improved.

Monitoring subject welfare during the conduct ofresearch is an area for improvement according to an article on the ‘ Ethical Issues during the Conduct ofClinical Trials’. The ethical conduct of a clinical trial does not end with thesignature on the informed consent form. The rights, interests, and safety ofresearch subjects must be protected continually throughout the

study duration. Subject safety monitoring is the responsibility of several groups, includinginstitutional review boards (IRBs) research ethics committees (RECs) investigatorsand their research staffs, sponsors, and data monitoring committees (DMCs).

TheIRB has many roles, including the task of reviewing reports of unanticipatedproblems (UAPs) and of adverse events (AEs). This is a very important taskbecause AEs can indicate whether the drug is harming the human body, whichmeans the trial can be stopped before it seriously damages anyone. A trial willbe stopped if there have been an excessive number of AEs in one of the studygroups. However, there are concerns withmonitoring AEs because sometimes it is unknown if the AE is due to the toxiceffect of the drug or due to the underlying illness of the patient. This isparticularly a concern in phase two and three of clinical trials because inthese phases the drug is tested on patients that are ill. For example, patientswho have advanced cancer and have received all possible current treatments oftenparticipate in clinical trials, therefore it may be unclear if some of theadverse effects are due to the cancer or the drug.

To determine the cause of anAE would “ require measuring the excess events in the intervention groupcompared with the AE rate in the control group which would require the receiptof aggregated data on AEs and the number of subjects currently enrolled in theclinical trial as a whole” 3. However, the IRBs don’t receive thisinformation; therefore they can’t determine the possible cause of an AEoccurring during the trial of a drug. Additionally, IRBs receive littleassistance on how to handle such reports. Regulatory inconsistencies can leadto confusion concerning what AEs must

be reported and how they should bereported. The reporting of AEs plays an integral part in preventing seriouscomplications, therefore it is essential that this is done faultlessly. Furthermore, given that there are lots of partiesinvolved in the conduct of a clinical trial, the following are recommended for system-wideimprovement: overlapping responsibilities and possibilities for communicationbreakdown and the ethical responsibility associated with research in humansubjects. The life of a volunteer should not be put at risk due to lack ofcommunication and complacency.

Moreover, participants in clinical research haverights which they should expect, including the following4:· Right to Informed consent · Shared decision-making· Privacy for research participants· Return of results· Right to withdraw The right to informed consent is widely accepted as anintegral part of ethical clinical research. Participants should understand thepurpose, risks, benefits, alternatives and requirements of the research. Nevertheless, empirical data show that participants often do not have a good understandingof the details of the research because the information is too complex. Personally I think this is unfair for the potential volunteers because in orderfor them to make an informed decision they should be completely clear with theside effects and other significant information about the drug. There is a needto balance the goal of being comprehensive with the amount and complexity ofinformation in order to give the participants the information they need tounderstand the study details and make an informed decision.

Additionally, another ethical concern with clinicaltrials, especially in phase 1 is that these volunteers are asked to accept riskin order to develop knowledge that may not directly benefit them. Also, the probabilityof progressing from Phase I to U. S. FDA (The Food and Drug Administration) approval(LOA) reveals that only 9. 6% of drug development programs successfully make itto market5. Consequently, it seems unjust that many of these individuals put themselves atrisk which may cause health problems for them later on in life for a drug thateventually doesn’t enter the market or benefit others.

One would think that allthe testing in laboratories and on animals would show clear data if the drug isbeneficial and worth proceeding to clinical trials. However, the way apotential treatment works in animals may not mimic what will happen in humans. According to CenterWatch, only about one out of every 50 drugs tested inanimals is determined to be safe and effective enough to test in humans. Thereare cases where the drug does not affect the animal dramatically, only minoradverse effects, but when tested in humans at a lower dosage the results prove differently, and the humans are affected seriously. A prime example of this is the famous TGN1412trial (phase one) that began at 8am on 14th March 2006 with 8 healthymale volunteers. Phase I trials are often referred to as “ first-in-manstudies” as they are the first stage of testing in human subjects. Theyare designed to determine the maximum amount of the drug that can be given to aperson before adverseeffects become dangerous and it normally takes place with a small group of healthyvolunteers. They are usually monitored until several half-lives of the drughave passed.

TGN1412 is a monoclonal antibody that was beingdeveloped as a new medicine for the treatment of B cell leukaemia andautoimmune diseases. Six volunteers were injected with the drug and two withplacebo. All of the men given the drug experienced cytokine release syndromeresulting in angioedema, swelling of skin and mucous membranes. The firstpatient was transferred to the Northwick Park hospital’s intensive care unit 12hours after infusion and after 16 hours all of the men were in the intensivecare unit; all six experienced multi-organ failure. Not only did this trialrise ethical concerns, but also highlights how clinical trials can be improvedwith regards to the safety of the volunteers.

However, the biggest question that arose from thistrial was “ What went wrong?” The answerto this question provides a platform for what improvements and precautions canbe put in place for trials involvingimmunomodulatory drugs (drugs that modify the immune response or the functioningof the immune system as by the stimulation of antibody formation or theinhibition of white blood cell activity)6, which are high risk drugs because they target the immune system and clinicaltrials in general. In a reportissued by the Medicines and Healthcare products Regulatory Agency concludesthat the serious adverse reactions experienced by the healthy volunteers werethe result of an “ unpredicted biological action of the drug in humans”. Nonetheless, I don’t think that is a acceptable reason for the failure of the trial. Thesevolunteers nearly died and it has caused them potential problems in later lifebecause on discharge some were warned they may suffer an increased risk ofcancers and auto-immune diseases. This reason may also be used in futureclinical trials when with enough

investigation another cause could be found. Nevertheless, other investigations show potentialreasons why the clinical trial was unsuccessful. The primary objectives were toassess the safety and tolerability of increasing single doses of TGN1412 inseparate cohorts and to assess pharmacokinetics (the movement of drugs withinthe body.) TGN1412 binds to and is astrong agonist for the CD28 receptor of the immune system’s T cell (these are asubgroup of white blood cells vital for…….

.) Being a CD28 agonist means thatTGN1412 stimulates the physiological function of CD28 causing more T cells tobe created (TH1 and TH2 cells). WHAT T CELLS DO……..

Th1 cells promote ‘ cellular immunity’ in hostdefence and are also involved in reactions such as transplant rejection. Th2cells promote ‘ humoral immunity’ by helping B lymphocytes to proliferate andsecrete antibodies. CD28 is the co-receptor for the T cell receptor; it bindsto the receptors on the interacting partner in reaction through one of itsligands (B7 family).

A ligand is an ion or molecule that binds to a centralmetal atom to form a coordination compound7. Thedose of TGN1412 given to the human volunteers induced a rapid and large releaseof cytokines, which are small protein molecules that transmit signals betweenimmune cells and tissue cells. A ‘ cytokine release syndrome’ was identified inall of the individuals who were given the drug, which is a rapid release ofcytokines causing organ failure. This did not occur in the trial with thecynomolgus monkey, the animal model chosen for studies to calculate the dosefor the first human

exposure to TGN1412, at a dose that was numerically 500times larger than that given to human volunteers.

This shows that the pre-clinical developmentstudies that were performed with TGN1412 did not predict a safe dose for use inhumans, even though current regulatory requirements were met.

1 World Health Organisation. http://www. who. int/topics/clinical_trials/en/ (Accessed 09/06/2017)2 https://en.

wikipedia. org/wiki/Tuskegee_syphilis_experiment (Accessed 11/07/2017)3 Silverman, H. (2007) Ethical Issues during the Conduct of ClinicalTrials. Proceedings of the AmericanThoracic Society, Vol. 4, No. 2 | May 01, 2007. http://www. atsjournals. org/doi/full/10. 1513/pats. 200701-010GC (Accessed 04/08/2017) 4 Clinical research ethics https://en. wikipedia. org/wiki/Clinical_research_ethics (Accessed 04/08/17) 5 Clinical Development Success Rates 2006-2015 -BIO, Biomedtracker, Amplion 2016 https://www. bio. org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016. pdf (Accessed 04/08/2017)6 https://www. merriam-webster. com/dictionary/immunomodulator (Accessed 05/08/2017)7 https://www. quora. com/What-are-ligands (Accessed 07/08/2017)