Table 1: Milestones in the development of medical ethics [created by Dr Bilal Jamil, Pakistan]

Table: Historical Events 'Ethical Hazards' and Evolution of Ethical Codes and Guidelines.			
Year	**Historical Events – Ethical Hazards**	**Reactions - Outcomes - 'Guidelines - Legislations'**	**Reference**
460 -370 BC		**Oath of Hippocrates**	https://www.pbs.org/wgbh/nova/article/hippocratic-oath-today/
1904	**Upton Sinclair's novel 'The Jungle'** exposed the appalling working conditions in the meat packing industry	Lead to **Pure Food and Drug Act** of 1906	https://www.britannica.com/topic/The-Jungle-novel-by-Sinclair
1932	**'The Tuskegee Study of Untreated Syphilis in Negro males'**	1972, Associated Press reporter carried the story leading to public outcry.	https://www.cdc.gov/tuskegee/timeline.htm
	Patients not properly consented; unaware of their disease - syphilis, nor knew the reason of the study. Study designed for six months was continued for 40 years. Even after penicillin became treatment of choice in 1947 were denied treatment.	1973, Out of court settlement between patients, their families and the US government.	
		1974, US Congress passed an act creating **National Commission for Protection of Human Subjects of Biomedical and Behavioral Research.**	
		1997, US President Bill Clinton officially apologized on behalf of the nation.	
1937	**Sulphanilamide Tragedy**. More than 100 people died by taking elixir of the drug in diethylene glycol.	1938, the enactment of **Federal Food, Drugs, and Cosmetic Act**. Manufacturers were required to test the drugs for safety and present the evidence to the FDA prior to marketing.	https://www.fda.gov/about-fda/histories-product-regulation/sulfanilamide-disaster
1944-47	Unethical, inhuman and brutal experiments on civil and war prisoners by the **Nazi's in World War II.**	Trial of doctors in Nuremberg (1946-1947), eventually penalized for unethical practice. A ten point code called the **Nuremberg Code, 1947** was introduced which made 'consent' of the participants mandatory. The code did not have any legal status, nor was it enforceable in any part of the world. However, it has formed the foundation on which later codes have been based.	'Trials of War Criminals Before the Nuremberg Military Tribunals Under Control Council Law No. 10. Vol2,pp. 181-182 Washington DC: US government Printing Office, 1949
1948		**The Universal Declaration of Human Rights (Dec. 10, 1948)** was also adopted and proclaimed by the United Nations after the atrocities of World War II and it further reiterated the human factor involved in medical experiments.	https://www.ohchr.org/EN/UDHR/Documents/UDHR_Translations/eng.pdf
1962	**Thalidomide**, a drug used to treat morning sickness, caused birth defects in pregnant women in Europe, Canada and other countries. The drug was not approved in the US.	To prevent similar devastation, Federal Food, Drug and Cosmetic Act was amended in 1962- **Kefauver-Harris Amendment.** It required a drug manufacturer to prove, scientifically, that the drug is effective and safe, besides consent of participant, premarketing approval and adverse effect monitoring.	https://www.gvsu.edu/cms4/asset/F51281F0-00AF-E25A-5BF632E8D4A243C7/kefauver-harris_amendments.fda.thalidomide.pdf

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1964		**Declaration of Helsinki**, by World Medical Association, was first adopted in 1964, and then revised in 1975, 1983, 1989, 1996, 2000, 2008 and 2013. It introduced the concept of independent committees to oversee ethical issues in research.	https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/
1966	**Henry Beecher**, reported 'ethical lapses' in research carried out in renowned universities and published in leading journals.	Emphasized the need for 'informed consent' and 'an intelligent, informed, conscientious, compassionate, responsible investigator'.	Beecher HK. Ethics and Clinical Research.The New Engl. J Med, 1966; 274: 1354–1360
1979		**The Belmont Report**, published by National Commission for Protection of Human Subjects of Biomedical and Behavioral Research. Three basic ethical principles for the protection of human research subjects-**respect for person, beneficence and justice.**	https://www.hhs.gov/ohrp/regulations-and-policy/belmont-report/read-the-belmont-report/index.html
1990		Inception of **The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)** at Brussels in a meeting between industry representatives and regulatory agencies from EU, Japan and the US.	
1995		Good Clinical Practice (GCP) guidelines by the WHO published.	https://www.who.int/medicines/areas/quality_safety/safety_efficacy/gcp1.pdf
1996		The Guideline Good Clinical Practice (GCP) "E6" developed and approved by the representatives from EU, Japan, United States, while Australia, Canada, Nordic countries and WHO were observers.	
2016		ICH-GCP revised. ICH-GCP 'E6' (R2)	https://database.ich.org/sites/default/files/E6_R2_Addendum.pdf
2018		FDA endorsed the GCP guidelines and accommodated them in federal regulations.	https://www.fda.gov/downloads/Drugs/Guidances/UCM464506.pdf E6(R2) Good Clinical Practice: Integrated Addendum to ICH E6(R1) Guidance for Industry U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) March 2018