Biomedical Engineering: Ethical Problems in Advanced Health Technologies.

First International Conference on «Collaborative Biomedical Engineering for Open-Source Medical Technologies», Pisa, 1-2nd September 2018

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Biomedical Engineering has to play a greater role in Ethical Aspects which is not fully considered

- Ethical aspects in Clinical Trials (*Ethical Committees* are directly involved)
- Ethical Aspects in the Development of Hardware & Software Biomedical Technologies

European Regulation on Clinical Trials: towards the harmonisation of standards on clinical trials

Regulation n. 536/2014, 16th April 2014, on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC **will enter into force on 2019**.

The Regulation will ensure a greater level of harmonisation of the rules for conducting clinical trials throughout the EU. It introduces an **authorisation procedure based on a single submission via a single EU portal, an assessment procedure leading to a single decision**, **rules on the protection of subjects and informed consent**, and **transparency requirements.**

It will also make it easier for pharmaceutical companies to conduct multinational clinical trials, which should increase the number of studies conducted within the EU. The general principle is (art.3):

*A clinical trial may be conducted only if: (a) the **rights, safety, dignity and well-being of subjects** are protected and prevail over all other interests; and (b) it is designed to generate **reliable and robust data***.

To improve data transparency from clinical trials, an **European public and accessible databank** of detailed abstracts (including final relations) will be available once **a final decision is taken for the market submission or an authorisation is rejected** .
No application disclosure will be anymore accepted among States Members. Strenghtpoints: **unique evaluation of a clinical trail, shared by all the Member States , unique portal and European database directly managed by (EMA)** and **unique access point for the documentation delivery and access**.

Ethical problems are becoming more and more important and pervasive in all human activities.

As far as Scientific Research is involved, there is also a «***utilitarian***» aspect to be considered: no scientific Journal publishes now a research, an experimental or a developmental paper in which ethical problems are involved (basically implying human subjects or animals), without the approval of an Ethical Committee or the employment of a proper protocol on animals.

Historical Issues:
Nuremberg Trial to Doctors (1946-1947)

Medical experimentation in Nazi Germany (1939-1945)

- Infection with malaria, tuberculosis, typhus.
- Involuntary sterilization.
- Artificial insemination.
- Freezing in ice water tanks.
- Radiation exposure.
- High altitude oxygen deprivation.
- Mustard gas.
- Surgical mutilation, unnecessary transplants.

➔ Nuremberg Trials & Nuremberg Code.

The ten points of the Nuremberg Code (May 1947)

1) Required is the **voluntary**, **well-informed**, **understanding consent** of the human subject in a **full legal capacity**.

2) The experiment should aim at **positive results** for society that cannot be procured in some other way.

3) It should be based on **previous knowledge** (e.g., an expectation derived from animal and pre-clinical trials) that justifies the experiment.

4) The experiment should be set up in a way that **avoids unnecessary physical and mental suffering** and injuries.

5) It should not be conducted when there is any reason to believe that it implies a **risk of death or disabling injury**.

6) The **risks** of the experiment should be in **proportion** to (that is, not exceed) the **expected humanitarian benefits**.

7) Preparations and facilities must be provided that adequately **protect the subjects against the experiment's risks**.

8) **The staff** who conduct or take part in the experiment must be **fully trained and scientifically qualified**.

9) The human subjects must be free to immediately **quit the experiment** at any point when they feel physically or mentally unable to go on.

10) Likewise, the medical staff must **stop the experiment** at any point when they observe that continuation would be dangerous.

BME problems : Strong Needs of New Regulations on MD and IVD MD

The new Regulations on Medical Devices

On 5 April 2017, 2 new Regulations on medical devices were adopted, and they entered into force on 25 May 2017. These replace the existing Directives.

Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on **medical devices**, amending Directive 2001/83/EC, Regulation (EC) No 178/2002 and Regulation (EC) No 1223/2009 and repealing Council Directives 90/385/EEC and 93/42/EEC

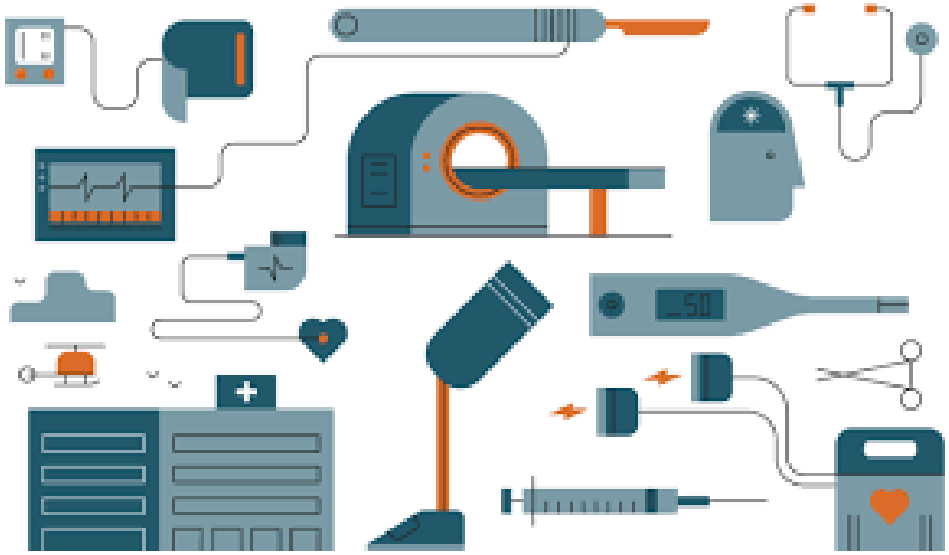
Regulation (EU) 2017/746 of the European Parliament and of the Council of 5 April 2017 on **in vitro diagnostic medical devices** and repealing Directive 98/79/EC and Commission Decision 2010/227/EU

The new rules will only apply after a ***transitional period***. Namely, 3 years after entry into force for the Regulation on medical devices (spring 2020) and 5 years after entry into force (spring 2022) for the Regulation on in vitro diagnostic medical devices.

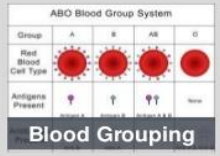
Ethical aspects have been a driving motivating source for the re-formulation of Medical Devices Standards

The need for a re-formulation of these **Regulations** came from serious incidents connected to deficits in medical devices (*silicon-gel mammary prostheses, metal-to-metal hip prostheses, etc*) happened in the last decades and which influenced a lot even European public opinion. The former legislation, based upon **Directives**, demonstrated to be unable to avoid these incidents.

i) Medical Devices and ii) In-Vitro Diagnostic Medical Devices



IN VITRO DIAGNOSTIC EXAMPLES



SEMOEGY

Australian Government
Department of Health
Therapeutic Goods Administration

Classification Examples

- Class 1 IVDs: Microbiological culture media; instruments/analysers
- Class 2 IVDs: Pregnancy self-tests, H&E stain
- Class 3 IVDs: sexually transmitted diseases; genetic tests (inc FISH)
- Class 4 IVDs: screen blood donors for infectious diseases; ABO typing

Regulation of In Vitro Diagnostic Medical Devices

The new Regulations on MD in a nutshell

The new Regulations contain a series of extremely important improvements to modernise the current system. Among them are:

stricter ex-ante control for high-risk devices *via* a new pre-market scrutiny mechanism with the involvement of a pool of experts at EU level

the **reinforcement of the criteria for designation and processes for oversight of Notified Bodies**

the inclusion of certain aesthetic devices which present the same characteristics and risk profile as analogous medical devices under the scope of these Regulations

the introduction of a **new risk classification system for *in vitro* diagnostic medical devices** in line with international guidance

improved transparency through the establishment of a comprehensive EU database on medical devices and of a device traceability system based on Unique Device Identification

the **introduction of an "implant card"** containing information about implanted medical devices for a patient

the **reinforcement of the rules on clinical evidence**, including an EU-wide coordinated procedure for authorisation of multi-centre clinical investigations

the **strengthening of post-market surveillance** requirements for manufacturers

improved coordination mechanisms between EU countries in the fields of vigilance and market surveillance

Summary of recent Regulatory Documents

World Medical Association (WMA) → Helsinki's Declaration (1964-2013, 7 releases)

1) Regulation (UE) n. 536/2014, «**On clinical trials on medicinal products for human use**»
2) Regulation (UE) n. 745/2017 (MDR), «**On Medical Devices**», repeals Directive 93/42/CEE (MDD)
3) Regulation (UE) n. 746/2017 (IVD), «**On In-Vitro Diagnostic Medical Devices**», repeals Directive 98/79/CEE (IDD)

1) Does not account for 2) e 3);

2) e 3) Do not recall ethical problems

Regulation UE 2016/679, 27th April 2016 mandatorily active from 25th May 2018, General Data Protection Regulation-GDPR

On the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation)

Health Data (anagrafic, from medical record, biometric, genetic)

DPO-Data Protection Officer (within 72h possible violations to be notified to Privacy Authority)

Accountability (to various levels)

For a complete implementation at least in Italy we will have a *National Law + Advice from Privacy Authority*

Status of BME in Italy

About **20** Italian Universities present a curriculum in BME (Bachelor/Master) and about **16** of Master only, with an estimated number of Students of about 5,000. Master-graduates about 900-1,000 per year. Placement is very good (93% employed after 1y, on-line with the other Engineering Degrees)

According to a recent Italian law, Biomedical and Clinical Engineers are acknowledged as professional figures in Health System after a Certification Process (still to be specified) carried out by the Engineer Order in agreement with Health and Justice Ministries.

Law 8.02.2013 – Italian Ministry of Health – Criteria for the composition and the operation of Ethical Committee

5. The composition of ethical committees must guarantee the qualification and experience necessary to evaluate ethical, scientific and methodological aspects of the proposed trials.

The members of ethical committees must possess a documented knowledge and experience in clincial trials related to drugs and medical devices and in the other matters of competence of the ethical committee.

At that purpose, ethical committees must include at least:

..omissis..

n) An expert on medical devices;

o) In relation with the medical area of reference for the trial of the medical device under study, a clinical engineer or other qualified figure

..omissis

Multidisciplinary composition of EC

Experts on Cardiology, Oncology, Oncological and Cardiac Surgery, Bioetic, Member of Health Professionists, Expert on Medical Devices, Genetist, Biostatistician, Representative of Volunteering and Patient Safeguard, Expert in Legal and Insurance matters, Pharmacologist, Pharmacist, Pediatrician, General Medicine Physician, etc…

Problems encountered «on-the-field»

Compromise between *scientific development* and *benefit* to the patient

Compromise between *privacy & security problems* and the advantage of *data-sharing*

Trials vs *placebo*

*Informed Consent [the **e-consent** is actually on studying]*

«*Precision Medicine*» vs «*Protocol-Based Medicine*» (!)

Ethical dilemmas (silicon-gel mammary prostheses, invasive therapies to CNS)

To think preliminarily of the *Patient* (example from Formula 1 cars); to find optimal tools of analysis: Google is better than OMS for the *prediction of flu epidemies (*!!??)

Fundamental message: Ethical problems must *NOT* be felt like a *constraint,* rather as a *developmental motor* to the *Innovation* (devices and instruments built «*people-oriented*»

Big Data in Health environment: important and unique role of BME

Data from EHR

Data from patient's vital signals which are online monitored

…

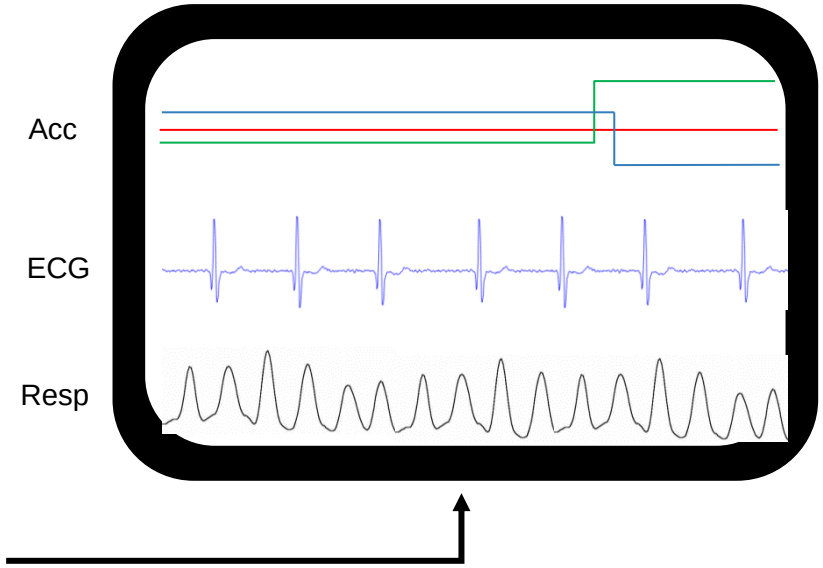
These data are well different from other kinds of «Big Data», i.e. inside Facebook or Amazon communities, etc.

Applicative software tools in Medicine and Biology is considered a «Medical Device» and therefore they must be treated by trained personnel.

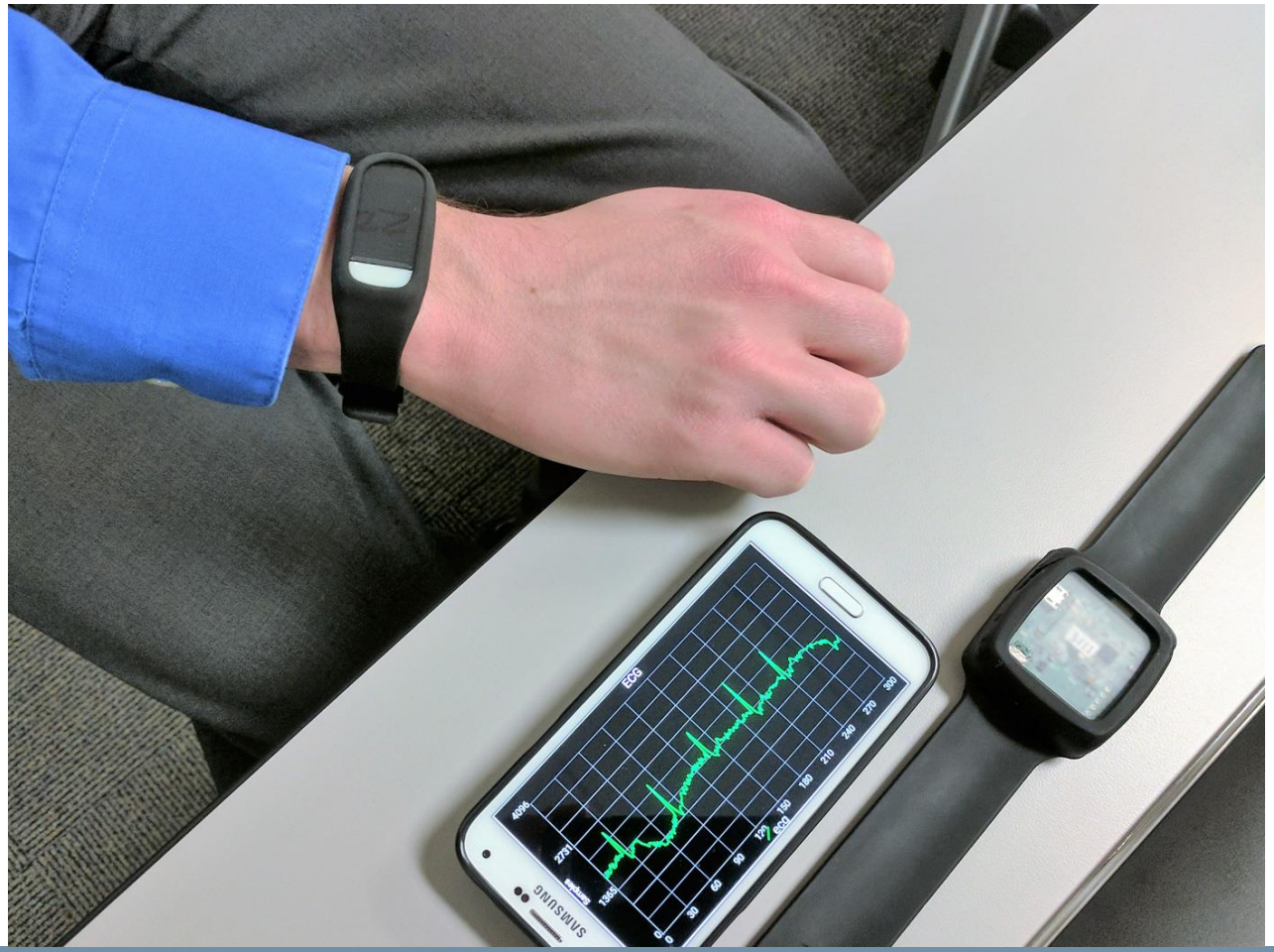
Sensorised T-Shirt

- Wearable device
- ECG, [24h: 170 k RR, 8 Mb] respiration and movements (accelerometers)
- Real time display on *tablet* or *smartphone*

Acquisition system and Bluetooth transmission of data to the *tablet*



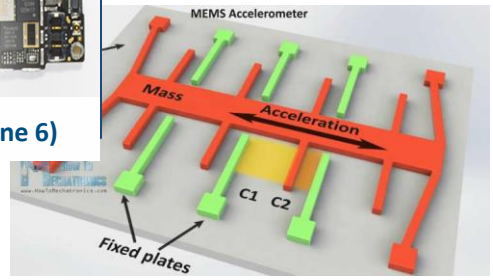
Smart watch for ECG detection



Mobile devices offer the possibility to **track the resting heart rate** for fitness purpose, thanks to externally-connected devices or to **embedded sensors technology**.

Camera-based Photoplethysmography

Accelerometer (Iphone 6)



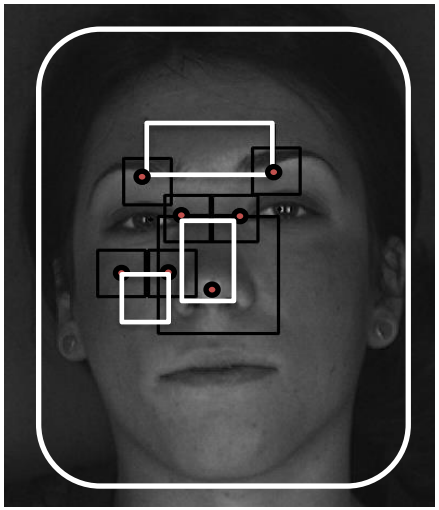
MEMS (Micro-Electro Mechanical System) **accelerometers**

MEMS 3-axis accelerometer consists of a mass suspended by 4 piezo-resistive beams at the center of the sensor chip. While accelerated, the mass causes the beams to deform thus changing resistance in the piezo material.
Also **3-axis gyroscopic devices** can be implemented.

Contactless medical devices

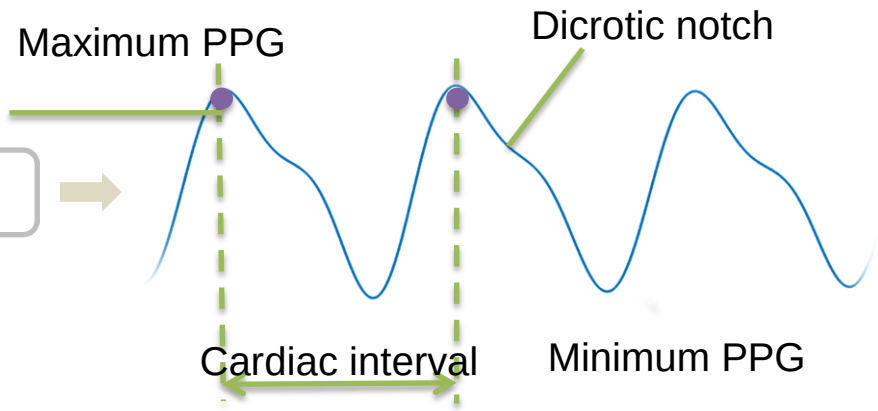
Face recognition

Fiducial points and PPG analysis



Processing

Video BVP



Big-cohort Studies

5 approved studies: **MyHeart Counts, mPower, GlucoSuccess, AsthmaHealth, Share-the-Journey** on a Open-Source platform (Research Kit, NEJM, March 2nd 2017)

70.000 participants enrolled in 7 months

MyHeartCounts → more than10.000 participants enrolled in the first 24h

ADAPTABLE (Aspirin Dosing: A Patient-centric Trial Assessing Benefits and Long-Term Effectiveness) → 20,000 subjects involved

DIGITAL AF (atrial fibrillation) study → more than 12,000 subjects and 120,000 recordings

Clinical trial involving an App Medical Device:, [Digital-AF Study, Antwerp, BE], e-Informed Consent

Digital-AF study

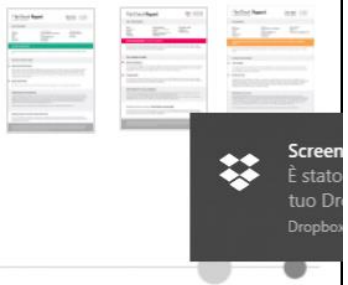
Local newspaper article
92 638 subscribers

Download the app
Create account
Scan QR-code

Information
60s recording
Symptoms

Steady position
2 measurements/day
1 week

Instant feedback
Centralized reviewing
Summary report



12 328
registered users
in 48 hours

120 446
60-second PPG traces
in 1 week

ESC Congress
Munich 2018

AI techniques applications: between correct and uncorrect information...

TO

LOGGED OFF Google can predict when you will DIE with 95% accuracy using AI

> The tech giant has developed a data-hungry computer system that hoovers up health info – and spits out details about your mortality

By Sean Keach, Digital Technology and Science Editor
19th June 2018, 3:14 pm | Updated: 19th June 2018, 3:15 pm

Methodological & Technological fundaments

From «Scalable and accurate deep learning with Electronic Health Record (EHR)»
Rajkomar A, et al, Digital Medicine, (2018), 1-18, May 2018

216,221 hospitalisation involving **114,003** unique patients taken from two Medical Centers: at the University of California, San Francisco (UCSF) and at the University of Chicago Medicine (UCM), **47 Billion [Gb]** data points.

Training set: **194,470**; Test set : **21,751**

In-hospital mortality (AUROC **= 0.94**)

30-day unplanned readmission (**0.76**)

Prolonged lenght of stay (**0.86**)

Final discharge diagnosis (**0.90**)

Towards an «Integral Ecology» [starting from «*Laudato si', sulla Cura della Casa Comune*», Encyclical of Pope Francis, 2015]

Concept of «Integral Ethics»: triad **Man, Animal, Nature** which has to be maintained for the wellbeing of **All**

«Unique Tale» on the origin of Universe and hence of our Planet

On our Planet there is **ONLY** one genealogic tree which gathers together **ALL** the **LIVING BEEINGS** (including Man)

The first Book that God wrote were not the **Holy Texts**, but the **Cosmos**

Ethical Committee, Politecnico di Milano

The EC operates with the objective to protect within the actual regulations:

a) The right, dignity, integrity, and well-being of human persons involved in the research
b) The respect of any other living organism
c) The respect of the environment in all its dimension and components
d) The freedom and promotion of Science.

The EC aims at providing opinions, evaluations and examinations to scientific investigators, to the structures directly involved and to the managemental bodies of the Politecnico in order to guarantee that the reseatch is carried out according to ethical principles of international and national standards, as well as from the Ethical Codex of the Politecnico itself, particularly for the researches concerning

- Human subjects
- Tissues or cells of human origin
- Personal data collection, concerning the treatment of information relative to a physical identified or identifiable person
- Animals
- Third countries
- Technologies of double use (i.e. possible alternative finalisation to military use, terrorism, etc)
- Technologies and information that could be used for non-ethical aims.

Ethical Committee of IRCCS Istituto Europeo di Oncologia e Centro Cardiologico Monzino, Milano

DM 8.2.2013, Law 189/2012.

The EC takes inspiration from the respect of physical integrity and human health, as indicated in the Chart of Human Rights, in the national Codices of Medical Deontology (2006), as well as at international level (Helsinki declaration – 1964 and successive releases and in Oviedo Convention of 04/04/1997, Law 28/03/2001, n. 145 (G.U. n. 95 of 24/04/2001).

Reference also to the Recommendations of Bioetics National Committee (Law 28/03/1990).

The EC is accredited from Region Lombardy AIFA/EMA and is controlled by the National Observatory on Clinical and Medical Trials.