RULEMAKING IN THE US

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2. List of abbreviations and central concepts

**Anonymized health data**: when personal identifiers irreversibly have been removed from health information preventing a person’s identity from being revealed. No link/code/key between the information and the subjects exists ensuring that data can never be re-identified.

**ANPRM**: advanced notice of proposed rulemaking

**Belmont Report**: published in 1979 by the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research under the full name “Ethical Principles and Guidelines for the Protection of Human Subjects of Research”

**Common Rule**: “The Federal Policy for the Protection of Human Subjects” (full name), applies to federally funded research involving human subjects. It was published in 1991 and codified in separate regulations by 15 Federal departments and agencies. The HHS regulations, 45 CFR part 46, include four subparts: subpart A, also known as the Federal Policy or the “Common Rule”; subpart B, additional protections for pregnant women, human fetuses, and neonates; subpart C, additional protections for prisoners; and subpart D, additional protections for children.

**Convened IRB review**: review by a full IRB

**De-identified health data**: when personal identifiers have been removed from health information preventing a person’s identity from being revealed. In HIPAA such identifiers include name, all geographic subdivisions smaller than State, birth date, telephone number, medical record number, biometric identifiers, mail address, IP address number and others. A link between the information and the subject may exist making it possible to re-identify the subject.

**Exempt study**: the study is not subject to the Common Rule (no IRB review necessary), but guidance by the OHRP recommends that there be some type of review by someone else than the investigator to confirm that the study qualifies as exempt, and many institutions do indeed impose such a requirement.

**Expedited IRB review**: review carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson. In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research.

**GDPR**: General Data Protection Regulation

**HHS**: Department of Health and Human Services

**HIPAA**: Health Insurance Portability and Accountability Act

**Human subject** (as defined in the Common Rule): a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.

**Identifiable information**: information where the identity of the subject is or may readily be ascertained by the investigator
**Informational harm:** the potential for harm or injury from disclosure of information about an identified individual

**IRB:** institutional review board. Each IRB shall have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the institution.

**Limited IRB review:** a term used in the Final Rule to describe an IRB review of projects under some of the exempt categories. The review are to focus on a few specific aspects of a study depending on which exempt category is relevant. Limited IRB review can be performed using expedited procedures.

**Minimal risk:** research activities where the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or test

**Non-identified:** a term used in the NPRM to distinguish it from the HIPAA term "de-identified." Non-identified biospecimens or data "have been stripped of identifiers such that an investigator cannot readily ascertain a human subject's identity" while HIPAA has specific requirements for what qualifies as de-identified. For all practical purposes non-identified and de-identified are identical concepts.

**NPRM:** notice of proposed rulemaking

**OHRP:** Office for Human Research Protection

**OSTP:** Office of Science and Technology Policy

**Private information:** information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, or provided for specific purposes by an individual and which the individual can reasonably expect will not be made public.

**Research:** a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

**Secondary research:** re-using information and biospecimens that are collected for some other “primary” or “initial” activity.
3. Mandate

Our mandate was to “evaluate the implications for Europe of the development in United States of a risk-based ethical review system for medical research aimed at replacing the Common Rule” (the Common Rule is the popular phrase for The Federal Policy for the Protection of Human Subjects in research). We have solved this task by describing the new legislation and review system in the US and how this affects biobanking and research on health data. We have further looked at the American research ethical debate on the new Common Rule. Finally, we have discussed pros and cons of the American research regulation compared to the typical European one. The project was conducted in the period of April 2017 to June 2018.
4. Summary

Since the Common Rule was developed in the 1990’s, the landscape and volume of research activities have changed dramatically. This growth and expansion of human subject research led to questions whether the regulatory framework was adequate and appropriate. The odyssey of revising the Common Rule began in 2011 with the Obama Administration. The goal was to update the current regulation “to better protect human subjects who are involved in research, while facilitating valuable research and reducing burden, delay, and ambiguity for investigators.” (ANPRM 2011).

As a first step in this effort, the Office of the Secretary of the Department of Health and Human Service (HHS), in coordination with the President’s Office of Science and Technology Policy (OSTP) published an advanced notice of proposed rulemaking (ANPRM). Among other things they proposed a refinement of the existing risk-based regulatory framework, an improvement of consent forms and the consent process, and the establishment of mandatory data security and information protection standards for all studies that involve identifiable or potentially identifiable data (ANPRM 2011). The most controversial suggestion was to expand the definition of human subject to cover research with non-identified biospecimens. This would mean that all secondary use of biospecimens would require an IRB review and a consent (NPRM 2015).

A majority of the public commenters strongly opposed this idea arguing that it would add little protection for the participants but a massive burden for the research enterprise. The Final Rule published in 2017 differed in important ways from these early ideas. Most significantly, several proposals were not adopted such as expanding the definition of human subject. Significant changes from the pre-2019 rule included new requirements regarding consent and consent processes, allowing broad consent for secondary research use of identifiable information and biospecimens, and new exempt categories based on their risk profile (Final Rule 2017). The Final Rule are to be effective from January 21, 2019.

In Europe, the general rule is to require consent and IRB review for secondary research on non-identified data and biospecimens. The introduction of GDPR from May 2018 strengthens the focus on consent. Although a comparison of systems is challenging due to the fundamental structural, constitutional and practical legal differences, it seems that the US and Europe are moving in different directions. The strengths and weaknesses of each regulatory system are discussed. In addition we investigate the implications for biobank research and cooperation across the Atlantic.
5. What are the main features of the Final Rule?

After more than 6 years of preparations, two proposed rules and two public hearing rounds, the Federal Policy for the Protection of Human Subjects (popularly called the Common Rule) were to be reformed. On January 19, 2017 - on the very last day of the Obama Administration - the Common Rule update called the Final Rule was issued. Most of the changes in the Final Rule were to be effective on January 19, 2018, but a couple of days ahead of this date an interim final rule delayed the effective date and general compliance date to July 19, 2018 and thereafter to January 21, 2019.

While the preparatory works were both innovative and ambitious based on clearly defined values and goals, the Final Rule might become best known for what it did not:

1. It did not adopt the most controversial proposal of defining research on non-identified biospecimens as research on “human subject” regulated under the Common Rule and thereby requiring consent.
2. It did not adopt the proposed standardized privacy safeguards for identifiable private information and identifiable biospecimens. Proposals that relied on such standards were either modified or rejected.
3. It did not substantially change the definition of “identifiable private information”.

However some of the proposed changes were upheld, including:

1. Allowing broad consent for storage, maintenance and secondary research use of identifiable private information and identifiable biospecimens. Doing research with broad consent on identifiable information and specimens is an alternative to conducting research without consent on non-identified information and biospecimens or obtaining consent for each specific study on identifiable private data or biospecimens.
2. New exempt categories of research based on their risk profile are introduced. However some of the new exempt categories, e.g. secondary research on identifiable private information or biospecimens, requires limited IRB review to ensure broad consent is obtained in accordance with the requirements.
3. New requirements regarding information to prospective research participants during the recruitment process, including information whether whole genome sequencing will be conducted, whether clinically relevant findings will be disclosed and whether biospecimens may be used for commercial profit.
6. US vs. Europe - who has the best research ethics for biobank research?

For the last seven years the US legislative authorities have been in the saddle of a major discussion about research regulation modernization, values and weighing of ethical principles. The result is a revised Common Rule that most likely will go into effect in 2019. What are the implications for Europe - if any? Can Europe learn something from the rulemaking process in the US? Is the US regulation of biobank research ethically superior or inferior to the typical European one? Will it change the premises for transatlantic research projects with either health data or biospecimens?

6.1 Risk based review

The new US regulatory framework for research could be characterized as unmitigated risk-based. Radical changes proposed during the rulemaking process were abandoned, and the Americans are left with a purer risk-based system than before. The key to understanding the US regulation is to see that physical risk function as the ultimate justification of research ethics, research regulation and ethical review boards. The main purpose of all these bodies, seen from a US perspective, is to protect research participants from research interventions that will expose them to unacceptable risks.

Research on already collected biospecimens and health data do not expose people to physical risks and will not involve any kind of intervention. This leads logically to the US position that biobank research, since it represents low-risk or no-risk research, should be “exempt” or involve a low level of regulatory burdens. This is of course a research friendly position, but based on the premise that physical risk is the *raisons d’être* for research ethical review, it follows that this position also represent the proper level of protection of research participant.

An important objection to the US regulation would be that “risk” must be understood as more than physical risk. Psychological, informational and privacy risks are all part of the research landscape as well. This topic was of course addressed in the US rulemaking process. In fact, one could argue that the concept of “informational harm” was one of the drivers for revision of the Common Rule in the first place. Privacy risks, though, has always been part of the picture in the US regulation. But there is a telling difference between the regulation of research on “identified” vs. “non-identified” data. Research on “non-identified” data do not - per definition so to say - involve any privacy risks. Since almost all biobank research will be performed on non-identified (de-identified) samples, this type of research will be exposed to few regulatory burdens.

Can your genomic sequence ever be called “non-identifiable”? This was a central question in the American debate. But there seems to be a notion in the US that a tightening of regulations should not occur before the “dangers” have been proven to exist. As long as the emerging informational risks and privacy risks are still considered as *mainly theoretical*, they will represent minimal risks for the participants in research that again justifies the continuation of a liberal regulation. In the end, the parties that tried to expand the understanding of human subject research and increase the focus on informational harm and privacy threats, lost the battle.
6.2 Privacy risks and GDPR in Europe

In Europe on the other hand, the regulatory system has put more weight on privacy- and informational risks. Data privacy is about fundamental human rights to privacy and protection. With the General Data Protection Regulation (GDPR) that came into effect May 2018 the existing law in Europe is taken a step further down the same road, facilitating even greater protection for individuals with a “citizen first” approach, including higher transparency, enhanced rights of individuals and strict limitation to data collection and sharing without consent. The regulation mainly applies independently of the context, and operates with strict enforcement and fines for breaches (European Union 2016).

By contrast, it can be argued that the US privacy legislation appears to be more fragmented and more concerned about the efficiency of data flow rather than the protection of individuals (Sandoval 2016). On a federal level, there is no single overarching privacy law but rather a sectoral approach towards legislation with the Health Insurance Portability and Accountability Act (HIPAA) as an example from the medical sector. The act describes privacy rules for individually identifiable health data. The various states also have some form of privacy legislation.

Even if we assume that privacy protection in practice is not worse in the US compared to Europe, the GDPR still represent a set of ideas that in the end was not met with public approval in the rulemaking process in the US. GDPR is not only concerned with protection. Equally important is the element of control. What GDPR aims for, is to put the citizens (or the research participants) in control of the use of their data. This represent a vision and values that go beyond simple protection of (research) data.

The US engaged heavily in the EU privacy debate preceding the GDPR. However, the EU lawmakers decided on a regulation miles away from the present future US law (Wuermeling 2016). One can find some of the same legal concepts in both European and US law, but most of the EU data protection rights described in the GDPR simply do not exist in the US (Boehm 2015).

6.3 Ethical review - why?

Even though Europe has put more weight on privacy and informational risks than the US, there seem to be more that separates the continents. In many European countries biobank research project will go through ethical assessment without any clearly articulated risk based justification. Research projects may be reviewed on the basis of their risk profile, but also on the basis that they belong to the category medical research. For members of ethical review boards, risk and protection of participants in research may be of great importance, for others the (lack of) scientific quality of the protocol would be the most pressing issue.

A common phrase is that “bad research is unethical research”. Ethical review boards may often feel justified to look into the quality of a research project in order to check if the risk participants are exposed to really can be justified by the supposed benefit of the research project. In sound ethical research the supposed total benefits must outweigh the risks. This logic, however, becomes problematic in non-interventional no risk studies. In such studies, where no harm can be done to participants and maybe also privacy risks are absent, there is no risk to be “justified” by the claimed benefit in the project. In such cases ethical review boards will transform from ethics committees to pure scientific committees. The justification for this transformation may seem unclear, and we have no guarantee that ethical review boards are the best to assess the quality of a project. The risk (!) of
an unclear justification for research ethical regulation is unnecessary obstacles for researchers and unnecessary hampering of potentially valuable research.

The Common Rule has a clear ethical justification. It is easy to see why and when ethical review is needed, what role informed consent should serve, why a project can be exempt and when and why a project might be eligible for an expedite review. It is all about risk and calibration of risk related to the nature of the research project.

6.4 US vs. Europe - who has the best research ethics?

The revised US Common Rule may be inspiring for European research regulation by its clear and stringent commitment to risk. Physical risk is the primary focus, since human subject research is defined as research involving intervention or interaction with human beings. Privacy risk is also part of the picture, but only as long as we are dealing with identified data. Non-identified (de-identified) data poses no privacy risk, and hence research on such data will be exempt.

A pure risk based system is elegant and easy to understand, with a clear idea of “what is at stake” in research ethics (protection of participants). It is also research friendly because it tries to minimize burdens for researchers, by expedite or exempt review processes in the case of low or no risk research.

European regulatory bodies should take interest in the American rule making, at least due to the fact that they have been through seven years of public discussion, with thousands of voices being heard, and with maybe some of the strongest bioethics scholars in the world involved in the debate. There is something to learn here. The fact that US and Europe are worlds apart in their research ethical regulation - that Europeans have a different view on what human subject research really is and a completely different view on how non-identified (de-identified) data should be regulated - should at least be met with curiosity.

Europe seems to have a more precautionary approach to privacy and informational risks. Whether the risks are purely theoretical or not, is however not necessarily the main issue in Europe. The principal point is that research participants (and citizens in general) should be in control of the use of their data. This ideal builds on numerous assumptions that philosophically can be questioned for the purpose of medical research (Is it important that donors of data and biospecimens in research feel that they are “in control”? In what sense are “my data” mine? In what sense are research on non-identified samples or data really research on me?). This is not the place to go into these discussions. The point is just to realize that Europe and US ended up with different answers to these questions. With the implementation of GDPR, being in control has gained even more footing in Europe.

A stronger focus on informed consent, purpose limitation, inspection rights, informational rights, transparency and ethical reviews, obviously hampers biobank research in the short run. The US regulation is more research friendly. If risk (and protection of participants) and not control is the dominant factor in research ethics, it is also possible to claim that the US regulation represents a proper protection of the interest of participants.

In the long run, however, we don’t know for sure which regulatory system represents the best research ethics. It might be the case that the future of biobank research is characterized by more re-contact and interaction between the biobank and it’s donors, more mutuality and partnership, more engagement, more electronic interfaces and dynamic consents, more choices, more return of results, more blurring of the distinction between research and care, more “My page”-solutions and
more sharing of data. If that is the future of biobanking - and it is hard to decide right now - then the Europeans seem well prepared. Participants must transfer from passive donors to active participants - and they should take control. The European regulatory system will fit such a future because it is rigged for the active participant. The system will generate trust and trusting participants will share more and participate more.

For now, the European model may run the risk of being overprotective and overambitious. The typical biobank donor still “participates” in a passive way - fitting very well the American category of non-human subject research.

6.5 Implications for trans-Atlantic research projects?

Seeing that the Common Rule underwent only minor modifications with regard to identifiability, the definition of “human subject” and exempt categories, the implications for cooperative research between Europe and the US are modest - if any. As before the Final Rule, data sharing might still represent a hindrance seeing that major American funding institutions like the National Institute of Health currently require data to be shared through semi-open databases. Several European countries on the other hand will not allow such a practice. The gap between the European and the US understanding of the terms non-identified/de-identified and anonymous adds to the complexity. In general, sharing of research data and biospecimens across the Atlantic still require careful consideration with respect to laws, ethical standards, issues of ownership and privacy safeguards.

In continuation of the above, the GDPR might also complicate research cooperation across the Atlantic. When transferring personal data to a country not subject to the GDPR the sending entity must ensure that the receiving country have equal or better data protections in place. Among non-EU countries, only a handful meet those criteria, and the US is currently not one of them (Eaton 2017).

In the following we will describe the lawmaking process in the US in greater detail, including the legislators’ proposals, the public comments, the ethical debates and the final outcome constituting the Final Rule. We believe that it could be of great value for European research institutions and regulators to gain insight into the details of the American debate, and how and why they ended up with solutions that is quite different from the typical trend in Europe.
7. A closer look on the new Common Rule and the rulemaking process

7.1 Background

U.S. Federal regulations governing the protection of human subjects in research have been in existence for more than three decades. Basic regulations were first published in 1974 by the Department of Health and Human Services (HHS, then Department for Health, Education and Welfare). A series of highly profiled abuses in research - among them the infamous Tuskegee-case - led to the enactment of the 1974 National Research Act which in turn led to the National Commission for the Protection of Human Subjects of Biomedical and Behavioral research (National Commission). In 1979 the Commission published “Ethical principles and Guidelines for the Protection of Human Subjects of Research”, also known as “the Belmont Report” (National Commission 1979). The Belmont Report identifies three fundamental ethical principles for all human subjects research - respect for persons, beneficence, and justice.

Respect for persons, according to the Belmont Report, comprises two separate moral requirements: “the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy” (National Commission 1979).

Beneficence is described as the goal of maximizing possible benefits of research and minimizing possible harms. Evaluating possible benefits requires examining the likelihood that knowledge would be generated and how important or useful that knowledge would be to society, but also identify the benefits for the particular research participant. In the Belmont Report beneficence is understood as an obligation affecting both researchers and the entire research enterprise.

Justice is described by the question “Who ought to receive the benefits of research and who ought to bear its burdens?”, in which the justice is about “fairness of distribution” or “what is deserved” (National Commission 1979).

Based on the work by the Commission, the HHS revised the regulation in the early 1980s. In 1991, 15 other Federal Departments and agencies joined HHS in adopting a uniform set of rules for the protection of human subjects in research; the Federal Policy for the Protection of Human Subjects. The HHS regulations, 45 CFR part 46, include four subparts: subpart A, also known as the Federal Policy or the “Common Rule”; subpart B, additional protections for pregnant women, human fetuses, and neonates; subpart C, additional protections for prisoners; and subpart D, additional protections for children.

For all participating departments and agencies the Common Rule outlines the basic provisions for institutional review boards (IRBs), informed consent, and Assurances of Compliance. The Common Rule describes how the principles of the Belmont Report may interplay and how researchers and IRBs should weigh and balance the often conflicting implications. The regulation also delineate criteria for, and levels of, IRB review. Unless research is determined to be exempt from the regulations, Federally funded research involving human subjects is reviewed by an IRB in one of two ways: 1. by a convened IRB or 2. through an expedited review process. Review by a convened IRB is the highest level of review, and is applied to most studies involving more than minimal risk and to many studies involving no more than minimal risk (see appendix 1). Expedited review by a single IRB member is the next level of review, and is applied to a study if the research appears on a list published by the Secretary of HHS of categories of research eligible for such review, and the research is found by the reviewer(s) to involve no more than minimal risk (see appendix 4). In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance
with the non-expedited procedure. The standard requirements for informed consent (or its waiver or alteration) apply regardless of the type of review - expedited or convened - utilized by the IRB. Exempt from IRB review means that a study is not subject to the Common Rule and no review is required. The regulations specify six exemption categories, but there must be some type of review by someone other than the investigator to confirm that the study qualifies as exempt, and many institutions do indeed impose such a requirement (ANPRM 2011, see appendices 2 and 3).

Although the Common Rule only applies to government-funded research, nearly all US academic institutions voluntarily adhere to the regulation (ANPRM 2011).

7.2 Why should the Common Rule be revised?

Although the Common Rule has been amended over the years, it has not necessarily kept pace with the evolving human research enterprise. Most people would agree that the landscape of research activities has changed dramatically since the Common Rule was developed, like changes in its volume, where it takes place, how researchers cooperate and share data, and how data is generated/obtained and analyzed (ANPRM 2011).

Just as technology evolves so does the nature of risks and benefits of participating in research. Some decades ago most studies involved interaction with the research subjects. Nowadays however, many studies are based on analyzing information obtained from medical records, education records, already collected research data, and existing biospecimens stored in various repositories. These kinds of studies represent mainly informational risk instead of physical risk; that is, harms would result primarily from the inappropriate release of information rather than the research interventions themselves (ANPRM 2011, NPRM 2015, Rothstein 2011).

As a consequence of the observed technological advancements, data that formerly were treated as non-identified can now be re-identified through combining large amounts of information from multiple sources in novel ways. There is also an increased use of sophisticated analytic techniques for use with human biospecimens, for instance in the field of genetics. (NPRM 2015). Thus, informational risk has grown, requiring caution to ensure that such research is subject to appropriate oversight.

Also, there has been a shift in prospective participants’ expectations to research. A growing body of literature show that people want to be asked for their consent before their health data and biospecimens are used in research (Kaufman et al. 2009, Vermeulen et al. 2009, Simon et al. 2011, Trinidad et al. 2011, Trinidad et al. 2012). The proper regulation of research on biospecimens and cell lines also became a major ethical issue in the American public debate after the Henrietta Lacks controversy in 2010, probably motivating the initiative to revise the Common Rule (Smith et al. 2017).

Because of this metamorphosis in research activities and technologies, and transition in public engagement expectations, a wide range of stakeholders raised concerns about the limitations of the existing framework. For instance, in 2001 the National Bioethics Advisory Commission made 30 recommendations for improvement (National Bioethics Advisory Commission 2011). Critical evaluation was also called for by the Institute of Medicine (Federman et al. 2002, Nass et al. 2009), the U.S. Government Accountability Office (Heinrich 2001) and many scholars (Emanuel et al. 2004, Kim et al. 2009). Additionally, in 2011 the President’s Executive Order required Federal agencies to review existing significant regulations to make them more effective or less burdensome in achieving
the regulatory objective (Executive Order 2011). Taken together, the stakeholders argued for “a re-evaluation of how the fundamental principles that underlie the Common Rule — respect for persons, beneficence, and justice — are applied in practice to the myriad new contexts in which U.S. research is conducted in the 21st century” (NPRM 2015).

7.3 The formal process of revising the Common Rule

In response to these changes and initiatives, an advanced notice of proposed rulemaking (ANPRM) were published in July 26, 2011 by The Office of the Secretary of the HHS in coordination with the Office of Science and Technology Policy (OSTP). More than 1100 public comments were submitted in response to the ANPRM. After four years of considerations, the HHS and 15 other federal departments published a Notice of Proposed Rulemaking (NPRM) on September 8, 2015. The ideas presented in 2011 had been further developed and refined in parallel with the dialogue with the public commenters regarding the changing nature of research and the preferred balance of protections for research participants among the principles of respect for persons, beneficence, and justice. The dialogue started with the 2011 proposals was also nourished by new empirical studies, several Federal initiatives and specific controversial cases in the US society. More than 2100 members of the public commented on the ideas put forward. The most commented proposals were related to biospecimens (Final Rule 2017). In the following we will elaborate on the discussed ideas and proposals of special relevance to biobank research, such as the definition of “human subject research” and the new thoughts on identifiability, risk calibration and consequently exempt categories. Also, new requirements of consent, including broad consent, are addressed.

7.4 The US understanding of “human subject research” vs. non-identifiability

In the pre-2019 rule, human subject was defined as “a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual, or (2) identifiable private information.” Furthermore, private information was defined as “information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.” (adapted from 45 CFR 46 Subpart A; the “Common Rule”)

If a researcher was given access to anonymized information or biospecimens (i.e. no key existed) already collected for other purposes, the research was not considered to involve human subjects as defined in the Common Rule. If a researcher was given access to non-identified information or biospecimens already collected for other purposes, the research was still not considered to involve human subjects as defined in the Common Rule as long as the researcher could not readily ascertain the identity of the individual to whom the non-identified information or biospecimens pertained because, for example:
1. the researcher and the holder of the key agreed on not releasing the key to the researcher under any circumstances, until the individuals are deceased;
2. there were IRB-approved written policies and operating procedures for a data management center or a repository that prohibited the release of the key to the researcher under any circumstances, until the individuals are deceased; or
3. There were other legal requirements prohibiting the release of the key to the investigator, until the individuals are deceased (Office for Human Research Protections 2008). Hence, such research would not be considered human subject research, and no IRB review or consent would be necessary.

On the other hand, if a researcher was given access to individually identifiable information or biospecimens, the research would be regarded as human subject research under the Common Rule. Depending on how the researcher handled the identifiable information and biospecimens further on, the study could be exempt or non-exempt. If the researcher de-identified the information or biospecimens, the research would not be exempt because the researcher would still have indirect access to identifiable information through the coding system/key. However, if the researcher instead chose to anonymize the identifiable information or biospecimens, i.e. record the information in such a manner that subjects could not be identified either directly or indirectly through identifiers linked to the subjects (= no key existed), the study would be exempt (Office for Human Research Protections 2008).

It is also worth noting that the Common Rule only applies to living individuals. Research involving information or biospecimens from deceased individuals would therefore not be subject to the Common Rule (Bledsoe and Grizzle 2013).

As it will appear in the following text, the pre-2019 rule does not differ noticeably from the post-2019 rule regarding the understanding of “human subject research” and non-identifiability.

7.5 Rethinking identifiability, the definition of “human subject” and consent for secondary research

In research projects were no interaction with the participant occurred, the meaning of “identifiable” and “readily ascertainable” became utmost important in determining if the research were covered by the Common Rule. Non-identified data and biospecimens could be used in research without meeting the regulatory definition of a human subject and consequently there would be no requirement for consent or IRB review. This is probably the case for a substantial share of biobank research. However, if the definition of “human subject” was met, the pre-2019 rule required IRB review and approval unless the study was exempt. A waiver of consent was permissible in certain cases if the criteria were satisfied (ANPRM 2011, see appendices 5 and 6). Hence, for researchers there was a profound difference in regulatory burden depending on whether the research data were considered identifiable or non-identifiable.

Both the 2011 and 2015 proposals asked whether it’s time to rethink the term identifiability and the definition of “human subject” in this context. What constitutes “identifiable” and “non-identifiable” data is fluid. Rapid advances in technology combined with the increased volume of data readily available may in the near future allow identification of an individual from data that is currently considered non-identified. As analytic techniques become more sophisticated and large datasets become more accessible, it might not be possible to guarantee that an individual could never be identified from a biospecimen, particularly if whole genome sequencing is conducted. Furthermore, regardless of what information is removed it is still possible to extract DNA from a biospecimen itself and potentially link it to otherwise available data to identify individual subjects. Hence, the 2011 and 2015 proposals considered categorizing all research involving the primary collection of biospecimens as well as storage and secondary analysis of existing biospecimens as research involving identifiable information and consequently research on “human subjects”. In other words, the proposal was to revise the definition of “human subject” to include research in which an investigator obtains, uses, studies or analyzes biospecimens, regardless of identifiability. The consequence would be a
requirement for informed consent for research involving biospecimens in all but a limited number of circumstances (ANPRM 2011, NPRM 2015).

This requirement for informed consent for secondary use of stored biospecimens was amplified by also referring to the majority of the public’s wishes, which reflected legitimate autonomy interests. In the NPRM, the legislators argued that beneficence is a powerful driver in research, and the support for research in the US is substantial. Yet members of the public deserve and expect knowledge on how publicly funded research is conducted and overseen, and need to be assured that the interests of research participants are adequately protected. Developing trust between researchers, funders, regulators and the public demands transparency (NPRM 2015).

The proposals in the NPRM were also shaped by the public comments submitted in response to more recent policy proposals such as “Draft Guidance on Disclosing Reasonably Foreseeable Risks in Research Evaluating Standards of Care” (Office for Human Research Protection 2014) regarding informed consent, “Request for Comments on the Draft NIH Policy on the Use of a Single Institutional Review Board for Multi-Site Research” (NIH 2014), the “Final NIH genomic data sharing policy” (NIH 2014) and the President’s “Precision Medicine Initiative” (The White House 2015) regarding participant-centered research. With the launch of the Precision Medicine initiative the relevant agencies hosted a series of roundtables and public workshops about public expectations on how participants want to engage in research. The discussions included individuals from multiple sectors including patients, prospective research participants, bioethicists, academic and industry investigators and technology innovators. The central position seemed to be that participants should be active partners in research and not merely passive subjects. The majority was seeking a research environment where they could contribute to the greater good but at the same time experience transparency into the research being conducted using their biospecimens and data (NPRM 2015).

During the same period the 2013 publication of the genome sequence of HeLa cell line (the immortalized cell line of Henrietta Lacks) caused controversy in the US society and many called for greater involvement of and respect for research participants (Goldstein 2017). Likewise, the case of the Havasupai Indian Tribe highlighted feelings of suspicion towards the research enterprise, especially among minority groups (Mello and Wolf 2010). These experiences emphasized the need to reexamine core values like trust, transparency and consent, particularly in the field of biospecimen research (Goldstein 2017).

In line with the arguments for consent for secondary research, several studies from the US indicated that while most individuals wanted to be able to decide whether their biospecimens should be available for research, they often did not desire to consent to each specific project. That is, they didn’t need to know which specific researchers use their samples, for which diseases and at which institution (Wendler 2006, Kaufman et al. 2009, Murphy et al. 2009). General/broad consent seemed to be an ideal compromise. The Secretary of HHS signaled they would develop a template.

However, an overwhelming majority of commenters (80 %) opposed changing the Common Rule to consider all biospecimens inherently identifiable – for various reasons. In general, commenters were particularly concerned with the burdens and the costs to collect, log and track consent status of data and biospecimens collected, and claimed it would be unmanageable for most institutions. Furthermore, they stressed that the research use of non-identified data or biospecimens does not involve risk to the research participant and called for convincing evidence of harm. Some also argued that the proposal would pose greater privacy risks than the current system because the consent form would be the only thing identifying the specimen. Several commenters also noted that although it is theoretically possible to identify a person based on non-identified data or biospecimens, the likelihood remains remote enough to argue against the presumption that all
biospecimens are identifiable (Final Rule 2017). They generally expressed the opinion that the existing regulatory framework was adequate and that current practices should be maintained, arguing that it would be an extreme change in response to an as yet unidentified or unclear problem. They were concerned that doing so would significantly slow advances in research and human health without adding meaningful protections for human subjects. In other words, they were not convinced that the principle of autonomy outweighed or trumped the principle of beneficence. The remaining 20% of the commenters were mostly individual members of the public who had the basic belief that donors should always be asked/consulted before using their biospecimens in research. One commenter simply noted that “research use of data initially collected for non-research purposes should always require informed consent.” (NPRM 2015) A majority of this group were also uncomfortable with the concept of broad consent. Those in favor of expanding the definition of “human subject” felt it would respect autonomy and individuals’ right to know and refuse, stressing the importance of anonymization of the specimens when used in research to avoid any negative consequences. Fractions of the group expressed a distrust of the medical and scientific research enterprise. Others expressed a desire to receive personal research results or to profit financially from discoveries (Final Rule 2017).

It is important to note that much of the opposing public’s concern was due to the assumption that the proposed changes would be applied retroactively. In response to comments after the first hearing round, as an effort to compromise with the public commenters, the NPRM proposed to have the new definition of human subject apply prospectively, and that compliance with this provision would be delayed until three years after publication of the final rule. It also said that if this primary proposal was too radical, an alternative model should be examined. Rather than considering all research using biospecimens as constituting human subjects research, the definition of human subjects could be expanded to include only specifically whole genome sequencing data, or any part of the data generated from whole genome sequencing (called alternative A). A second alternative model was to expand the definition of human subjects research to include the research use of information that is bio-unique (called alternative B). This was a somewhat broader scope than the first alternative model because it includes also other technologies than whole genome sequencing (NPRM 2015).

Few commenters explicitly preferred proposal A or B over the pre-2019 rule. However, the Presidential Commission for the Study of Bioethical Issues supported proposal B arguing it was the most forward-looking of the three suggestions and that one should avoid tying the definition of “human subject” to a particular kind of data but instead focus on the technology’s ability to identify donors (Final Rule 2017).

The legislators decided to not implement the proposed expansion of the term “human subject” to include all biospecimens regardless of identifiability. The premise behind the proposal was that continuing to allow research on biospecimens collected without consent was not consistent with the majority of the public’s wishes. Still, the comprehensive consultation rounds created enough ambiguity to doubt this premise (Goldstein 2017). Instead of including the initial proposal, the Final Rule included a new process by which the Common Rule departments and agencies regularly (at least every 4 years) assess whether new developments within the scientific landscape calls for reconsideration of how identifiability of either information or biospecimens is interpreted. It is expected that whole genome sequencing will become one of the first technologies to be evaluated in this respect (Final Rule 2017).
Rethinking how to calibrate the level of review to the level of risk

Risk in research can roughly be categorized into physical, psychological and informational risks. Other risks such as legal, social and economic harms would usually be considered variants of the three core categories. Physical risks are characterized by short term or long term damage to the body and include pain, bruising, infections or even death. Psychological risks could be defined as emotional or cognitive disturbances including anxiety, stress, sadness or depression. Informational risks exist when information is used inappropriately or disclosed, which in turn could be harmful to the study subject/participant or groups of subjects (Nass et al. 2009). Both the 2011 and 2015 proposals recognized that informational risks are becoming increasingly relevant. IRBs evaluate all three of these risk categories, but it is unclear if IRB members are equipped with the expertise necessary to adequately evaluate privacy and confidentiality risks (ANPRM 2011, NPRM 2015).

Based on communication with the regulated community, the policy makers launched the idea that standardized data protections, rather than IRB review, may be a more effective way to minimize informational risks. Consequently, the proposals suggested mandatory data security and information protection standards for all studies that involve collection, storage, analyzing and secondary use of identifiable or potentially identifiable data, including research with biospecimens. This would apply for both electronically stored and paper based information as well as information contained in a biospecimen. The proposal would not alter IRBs’ role in assuring that the ethical principles are adequately fulfilled. A fortunate bonus would be a decreased regulatory burden since IRBs would not have to evaluate informational safeguards for every single research project.

Since new mandatory standards for data security and information protection was suggested, only non-informational risks would be considered in determining the level of risk posed by a research study. The following changes were considered (ANPRM 2011):

1. Requiring written broad consent for secondary research use of any biospecimen collected for purposes other than the proposed research. The use would not require IRB review but would be subject to the data security and information protection standards mentioned above. This was already permissible in some cases under the Common Rule, but in conflict with the HIPAA Privacy Rule and therefore has not been practiced.
2. A revised approach to expedited review, including expanding the current exempt category 4 (regarding the collection and use of existing data and biospecimens) to include all secondary research on identifiable data and biospecimens already collected for other reasons than the proposed research, provided a broad consent as described above.
3. Eliminating the requirement of routine annual continuing review of expedited studies.
4. Streamlining submission requirements.
5. Eliminating the requirement for continuing review of studies where the remaining activity were limited to either 1) data analysis or 2) accessing follow-up clinical data from procedures that the participants would otherwise undergo as part of standard care for their medical problems.

Roughly 130 commenters addressed the proposed mandatory standards for data security and information protection, with the majority supporting it, although most commenters pointed out the difficulty of evaluating standards not yet developed. Commenters opposing the proposal argued that inclusion of standards in the Common Rule were redundant since patient information is already covered by HIPAA and other regulation, and that the wide range of research activities would make it too challenging to develop a blanket standard. Those in favor of the proposal argued it would engender consistency across IRBs in how informational risks were handled, and underscored that the HIPAA standards are appropriate for health information but not for other types of research data.
Despite the majority of supportive comments, the Final Rule did not adopt the proposal. The legislators continued to underscore the importance of protecting research participants’ privacy and preventing security breaches, but also acknowledged the public’s concern of adhering to standards not yet developed. Rather than issuing standards lacking sufficient specificity to address the variety of informational risks arising in research today and the years to come, the legislators decided it would be preferable to continue to leave these issues in the hands of IRBs. However, the Final Rule includes a commitment that the Secretary of HHS will issue guidance to assist IRBs to identify appropriate protections to ensure privacy and confidentiality for research subjects. This guidance would for instance take into consideration the level of identifiability and sensitivity of the collected information (Final Rule 2017). As a consequence of not implementing the proposed standards, some of the suggested exempt categories that relied on the standards will instead require limited IRB review. The relevant exemption categories include

- the exemption for the storage or maintenance of identifiable private information or identifiable biospecimens for which broad consent is required, when there is a change specific to the research activity in the way the material is stored and maintained (§104(d)(7)), and
- the exemption for the secondary research use of identifiable private information and identifiable biospecimens for which broad consent is required (§104(d)(8)).

A limited IRB review, according to the Final Rule, means that an IRB may use the expedited review process. Also, as suggested in the NPRM, an evaluation of the list of expedited review categories will take place every 8 year, followed by publication in the Federal Register and accompanying public comments.

### 7.7 Rethinking exempt categories

Significant portions of health research in the US are exempt (Loe et al. 2016). Exempt and non-exempt research are handled very differently. Under the pre-2019 rule, non-exempt research required full IRB approval, and (even without changes) continued review at least once per year. However, if a research activity fell under an exempt category it would be fully exempt from the regulations. It was not specified how one should proceed to determine whether research was exempt, but the Office of Human Research Protection (OHRP) recommended that researchers should not make that determination themselves. In practice, local IRBs and their staff were the decision makers, making “exemption” functioning as a third level of IRB review in addition to expedited and full review (Loe et al. 2016). One of the exempt categories included the collection or study of existing individually identifiable data, documents, records, or pathological or diagnostic specimens if sources were publicly available or if information was recorded so that subjects could not be identified in any way, i.e. the data and biospecimens would be anonymized (= no key existed).

The NPRM proposed to add new categories of exempt research. All the pre-2019 exemptions were retained, but the NPRM proposed reclassifying some of the exempt categories as exclusions not subject to IRB review, and the remaining categories as exempt subject to certain regulatory requirements - in contrast to the pre-2019 rule’s definition of exempt. The NPRM also proposed recategorizing the exemptions into three groups according to the type of risk characteristically involved and what protections (e.g. consent or privacy safeguards) were needed:

1) low-risk interventions with no requirements
2) activities requiring privacy safeguards
3) secondary research with identifiable private information or biospecimens requiring privacy safeguards, broad consent and limited IRB review. The IRB review would then aim at reviewing the process of obtaining consent, and ensuring that protection standards were met.

The term “low-risk” denoted research activities that do not involve physical risks, and where the magnitude and probability of other risks are assumed to be minimal. The rationale behind requiring broad consent for the secondary use of identifiable biospecimens was honoring the principle of respect for persons without reducing the principle of beneficence notably. The exemption would only apply to research proposals were individual research results were not to be returned to the research subject. If a researcher did not plan to return results, but later decided opposite, an IRB would have to review and approve the plan for returning the results to the subjects.

A total of 150 commenters addressed the proposals involving broad consent for secondary research with identifiable private information or biospecimens. A majority of the commenters agreed that identifiable biospecimens should be a part of the exempt categories. There was a general support for creating a pathway for minimal risk research to occur without IRB review, but a majority opposed that this exemption would be the only way besides study specific consent for research on biospecimens. Several of the public’s pros and cons regarding expanding the definition of “human subject” appeared also here, with a majority indicating that this was not the best way of balancing respect for persons with facilitating research.

Those who opposed the exemption argued that IRBs assess more than privacy and confidentiality issues and whether informed consent is sought and obtained. Some commenters, that also supported the expansion of the definition of “human subject”, were mostly members of the public who argued that study-specific consent was the only viable road. They felt that broad consent would not respect the research subjects because they would have no knowledge about the research activities. Others argued that broad consent (as opposed to no consent) introduced new privacy and confidentiality risks to subjects not present under the pre-2019 rule because it demanded the retention of identifiers required to track which specimens could be used for research.

The legislators also suggested to allow researchers to make exemption determination themselves, but only if aided by a web-based tool for automated determination - due to considerations of a conflict of interests. The tool was yet to be completed. The idea was to free IRBs from time-consuming activities adding little value to the protection of research subjects, and thereby increasing available time for applications for more risky projects. However, the determinations had to be documented at an institutional level. The Final Rule did not adopt the proposed documentation requirements for how exempt determinations were made, but announced that the development of an exemption decision tool would continue to be explored.

7.8 Secondary use of identifiable information and biospecimens without consent

As mentioned above, the Final Rule term “exempt” do not always mean exempt from all of the requirements of the Common Rule. The Final Rule list some exempt categories (at §___104(d)(4)) in which identifiable private information and biospecimens can be used for secondary research without requiring consent. This requires that

1) either the data and biospecimens are publicly available,
2) the identity of subjects is recorded by the investigator in such a way that the identity cannot be readily ascertained and the researcher do not try to contact or re-identify subjects,
3) the research is regulated under HIPAA, or
4) the research is conducted by or on behalf of a federal entity where the original collection was subject to specific privacy protections.

Typically, the information or biospecimens covered by this exemption would be found in some type of records or tissue repository at a hospital; i.e. it does not cover any primary collection. The Final Rule provision 1 and 2 in the list above differs from the pre-2019 rule by allowing the exemption to include research with information or biospecimens that do not yet exist on the onset of a study (i.e. that could be collected in the future for purposes not related to the proposed research study). The provisions 3 and 4 have no precursors in the pre-2019 rule.

These new rules allow researchers to see and store identifiable private information and identifiable biospecimens as part of their research records, effectively acknowledging that IRB review would not add any protection/reduce the risk for the participants. Note that this exemption only address identifiable private information and biospecimens, since the early proposals of expanding the definition of “human subject” to include non-identified biospecimens was not adopted. Therefore an exemption for such material was not needed.

7.9 Secondary use of identifiable information and biospecimens requiring broad consent

The Final Rule also includes two exemptions (at §___.104(d)(7) and §___.104(d)(8)) related to storing, maintaining and use of identifiable private information and identifiable biospecimens for secondary research requiring broad consent. Again, the exemptions pertain only to reusing information and biospecimens collected for some other “primary” or “initial” purpose.

The Final Rule expands the proposed limited IRB review to include an evaluation of the process through which broad consent will be obtained, whether the broad consent includes all the required elements, if the broad consent is appropriately documented, that the research to be conducted is within the scope of the broad consent and that the researcher does not plan to return research results. If a change is made for research purposes in the way the identifiable information or biospecimens are stored or maintained, IRB must ensure that adequate provisions are in place to protect the privacy and confidentiality of the participants’ data. Such changes could be e.g. if information or biospecimens will be stored for longer than they otherwise would have been for the original purpose, or if information or biospecimens are placed in a registry or repository created to serve as a resource for other researchers. Thus, relevant changes are those changes that would alter risks to the privacy or security of the stored material, including giving access to or transferring material for research purposes to someone who otherwise would not have access.

The legislators’ rationale behind this exemption category is to respect the research subjects’ autonomy and provide appropriate privacy safeguards without imposing an invincible administrative burden even if it involves the potential risk of having identifiers associated with the data and specimens. It is also responsive to those commenters pleading that IRB oversight should be retained for the secondary use of identifiable private information and identifiable biospecimens (Final Rule 2017).
7.10 Rethinking the informed consent process

Various aspects of the consent forms had been heavily criticized. The Common Rule requires that the consent forms include at least eight specific items of information. However, as time has passed the consent forms had grown in length (often between 15-30 pages), become more legalistic and with a high reading level, even for relatively routine and low risk research studies. Its content had been criticized to function as sales documents instead of genuine aids to good decision-making, and inhibited people from understanding relevant information. Suggested changes described in the ANPRM included increasing the specificity of the content, restricting inappropriate content, limiting the length of various sections, prescribing how information should be presented in consent forms, reducing institutional “boilerplate” (i.e. standard language to avoid lawsuit), and making available standardized consent form templates (ANPRM 2011).

Both the ANPRM and the NPRM suggested that regulatory text should emphasize the need to start an informed consent sheet with essential information a reasonable person would need in order to make an informed decision (including explaining why someone might not want to participate), not to mention facilitating the subject’s understanding of the consequences of participation.

Almost all of the approximately 200 commenters addressing informed consent requirements supported the intention behind the suggested revisions, and a majority supported the proposals. Several commenters expressed a desire to share in the profits of successful innovation based on their data and biospecimens, and stated that the commercial aspect of a research plan could be important in their decision making process. Others described their disappointment when realizing research results were not returned, underscoring the need to include such information during recruitment of subjects.

The Final Rule adopts almost all of the NPRM proposals to clarify and improve the general requirements for informed consent forms and the recruitment procedure. The general requirements include to inform potential research participants (when appropriate)

1. that identifiers might be removed from identifiable data and biospecimens and be used for future research without a new consent.
2. if identifiable data or biospecimens might not be used for future research studies (even if identifiers are removed).
3. that their biospecimens (even if identifiers are removed) may be used for commercial profit and whether the participant will or will not share the potential profit.
4. whether clinically relevant research results (including individual results) will be disclosed, and if so, under what conditions.
5. whether research on biospecimens will (if known) or might include whole genome sequencing (Whole genome sequencing is defined as the sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen.).

Information about whole genome sequencing was justified by the fact that this technique generates an enormous amount of information about a person, it provides insight into the health of individuals as well as their biological family members, and it may also reveal information (planned or unanticipated) years later. Such information in consent forms was also common under the pre-2019 rule, but there were some ambiguity which is now removed.

The NPRM proposal that was not implemented in the Final Rule was the requirement to provide potential participants with an option to consent or refuse to consent to being re-contacted by the
researcher. Re-contact could be relevant to seek additional information or biospecimens, or to recruit the subject for another research study. The public commenters questioned the importance of such information, and argued it would represent a substantial cost for tracking systems without adding any protection for the subjects. The legislators agreed and deleted the proposal.

7.11 Does an IRB need to review plans to return results to subjects?

It is generally recognized that in some studies, e.g. genetic studies, researchers are likely to come across information relevant to participants in terms of making decisions about their health care. For instance, one could learn that a man had a gene mutation significantly elevating his risk of getting familial hypercholesterolemia even though the finding was not necessarily related to the aim of the study (NPRM 2015).

The NPRM did not impose any requirements to share such knowledge with the participants, given the informed consent form did not promise any such feedback. On the contrary, if a researcher did have a plan for returning clinically relevant results to the participants, the IRB would have to evaluate the appropriateness of the plan. The NPRM suggested, as an alternative proposal to IRB review, that a federal panel of experts should be formed to decide which unexpected findings should be disclosed to participants in research. As a consequence, such studies could still be exempt as long at the disclosures were made consistent with the rules outlined by the federal panel (NPRM 2015).

Several commenters opposed the proposal that the exempt category could not be used if the researcher planned for return of results and regarded the idea as a disincentive to return results. They further argued that patients are entitled under HIPAA to know the content of their medical records and therefore investigators must always be prepared to return results to participants. Hence the proposal was at odds with existing law. However, others supported the idea of IRB review of researchers’ plans for returning research results, stressing the complexity of decisions in these matters (Final Rule 2017).

A little less than 20 commenters addressed the suggestion of a federal panel of experts, and the opinions were mixed. However, many called for a detailed guidance addressing what is an adequate plan in this context but some suggested erasing the proposal due to lack of clarity of IRBs’ role in such a review.

The Final Rule did not adopt the NPRM proposal of the need for IRB review of plans to return clinically relevant results to research participants. The reversal was justified by concern of the difficulty of making relevant criteria required for an IRB to perform such a review, the need for particular IRB expertise, and ambiguity over the meaning of “clinically relevant” (Final Rule 2017).

7.12 Some thoughts on the rulemaking process

In 2015 Kathy Hudson, the first executive director of the Patient Centered Research Foundation, called the ANPRM and NPRM proposals “long-overdue” and concluded that the reform “should help the scientific community take a giant leap forward in showing respect for research participants, without whom the biomedical research enterprise would cease to exist” (Hudson and Collins 2015).

While the 2011 and 2015 proposals for a revised Common Rule were based on a relatively clear idea that one ought to change how the ethical principles of the Belmont Report should be weighed as the landscape of research was changing, the product of the rulemaking process does not echo this idea in a convincing manner. When the rulemakers abandon the most controversial suggestions, they do
so due to the opposition from the commenters and not by arguing that the premises behind the ideas were flawed or confused.

Voices have criticized the final outcome of the controversial proposals regarding consent for secondary use of data and biospecimens independent of identifiability. Bioethicist Henry T. Greely of Stanford Law School concluded it was “a predictable result of the disparity in lobbying power” between the research enterprise and patient groups (Kaiser 2017). Melissa Goldstein, a former assistant director for bioethics and privacy in the White House Office of Science and Technology Policy, said it was unclear “whether the Administration decided that its original goals were truly unachievable or misguided, or whether regulators simply ran out of time or bargaining power” (Goldstein 2017).

Moreover, critics have raised important questions about the proper level of deference that regulators should give to public comments given the abrupt change in reasoning in revising the Common Rule on this matter (Goldstein 2017). Seeing that the consultation rounds created doubt about the underlying premise for the proposal, the legislators withdrew the proposal in its entirety. According to Goldstein (2017) it seemed that the rulemakers simply weighed which side in the debate generated most support from the commenters, and concluded accordingly. In contrast to the opinions expressed in the public comments, survey research has substantiated the notion that individuals will allow research on their biospecimens, but they want to be asked for permission (Rothstein 2010). According to Goldstein the legislators made no effort to weigh the disinterests/conflicting interests against each other, but merely based the policy reversal upon the public comments “and does not address the ethical issues underlying the need for change in the first place or explain and justify their abandonment” (Goldstein 2017).

Having said this, it is important to note that the ethical scholars and experts themselves ended up on both sides of this controversy. It was not ethics on one side, and the power of research interests on the other. For those ethicists ending up defending the Final Rule, the core argument was that increased research burdens were not justified from an ethical point of view where protection of participants is the most pressing issue. In the same way that the critics whole-hearted felt that the ethics was sacrificed with the Final Rule, the same way the defenders whole-hearted felt that the ethics won. This final point can be illustrated by the words of Ellen Clayton, a bioethicist and lawyer at Vanderbilt University in Nashville, Tennessee, expressed in an interview with Nature after the lawmaking process had come to an end; “I went into my chair’s office and did a happy dance, I’m thrilled” (Reardon 2017).
8. References

Appendix 1: Is an activity research involving human subjects?

Start here.

Is it research?

Is the activity a systematic investigation designed to develop or contribute to generalizable knowledge? [45 CFR 46.102(d)]

Activity is research. Does the research involve human subjects?

Does the research involve obtaining information about living individuals? [45 CFR 46.102(f)]

The research is not research involving human subjects, and 45 CFR part 46 does not apply.

Is the information individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information)? [45 CFR 46.102(f)(2)]

Activity is research involving human subjects. Is it covered by the regulations?

Does the research involve intervention or interaction with the individuals? [45 CFR 46.102(f)(1), (2)]

Activity is research involving human subjects. Is it conducted or supported by HHS? [45 CFR 46.101(a)(1)]

Is the information private? (About behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, or provided for specific purposes by an individual and which the individual can reasonably expect will not be made public.) [45 CFR 46.102(f)(2)]

Does the institution hold an FWA under which it applies 45 CFR 46 to all of its human subjects research regardless of the source of support?

The research involving human subjects is covered by the regulations.

Unless exempt under 45 CFR 46.101(b), 45 CFR part 46, subpart A applies to the research, and as appropriate subparts B, C, and D also apply.

The research involving human subjects is NOT covered by the regulations.

Go to Chart 2 AND

Other Federal, State and local laws and/or regulations may apply to the activity. [45 CFR 46.101(f)]

February 16, 2016

Appendix 2: Is the human subjects research eligible for exemption?

From Chart 1

Has HHS prohibited exemption of the human subjects research?  
(All research involving prisoners, some research involving children.)  
[Footnote 1 to 45 CFR 46.101(i), 45 CFR 46.401(b)]

NO

Will the only** involvement of human subjects be in one or more of the following categories?

Research conducted in established or commonly accepted educational settings, involving normal education practices?

YES

Exemption 45 CFR 46.101(b)(1) may apply.

Go to Chart 3

If not exempt under (b)(1)

Research involving the use of educational tests, survey procedures, interview procedures, or observation of public behavior?

YES

Exemption 45 CFR 46.101(b)(2) or (b)(3) may apply.

Go to Chart 4

If not exempt under (b)(2) or (b)(3)

Research involving collection or study of existing data, documents, records, or pathological or diagnostic specimens?

YES

Exemption 45 CFR 46.101(b)(4) may apply.

Go to Chart 5

If not exempt under (b)(4)

Research studying, evaluating, or examining public benefit or service programs?

YES

Exemption 45 CFR 46.101(b)(5) may apply.

Go to Chart 6

If not exempt under (b)(5)

Research involving taste and food quality evaluation or consumer acceptance studies?

YES

Exemption 45 CFR 46.101(b)(6) may apply.

Go to Chart 7

If not exempt under (b)(6)

No exemptions to 45 CFR part 46 apply.  
Provisions of 45 CFR subpart A apply, and subparts B, C and D also apply if subjects are from covered vulnerable populations.

Go to Chart 8

** "Only" means that no non-exempt activities are involved. Research that includes exempt and non-exempt activities is not exempt.

Appendix 3: Does exemption 45 CFR 46.101(b)(4) (for existing data, documents, records and specimens) apply?

**“Only” means that no non-exempt activities are involved. Research that includes exempt and non-exempt activities is not exempt.**

* Note: See OHRP guidance on research use of stored data or tissues and on stem cells at http://www.hhs.gov/ohrp/regulations-and-policy/guidance/guidance-on-research-involving-stem-cells/index.html, and on coded data or specimens at http://www.hhs.gov/ohrp/regulations-and-policy/guidance/research-involving-coded-private-information/index.html for further information on those topics.

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Appendix 4: May the IRB review be done by expedited procedures?

From Chart 2, or 7

Has the research been previously reviewed and approved by the IRB?

YES

No more than minimal risk to human subjects AND does the research involve only procedures included in categories 1 through 7 on the list of categories of research that may be reviewed through an expedited review procedure? [45 CFR 46.110(b)(1)]

YES

Is the research classified? [Paragraph (D) of Categories of Research That May Be Reviewed By an IRB through an Expedited Review Procedure.]

YES

Research is eligible for IRB review through expedited procedures. Agency head may restrict, suspend, terminate or choose not to authorize an institution's or IRB's use of the expedited review procedure. [45 CFR 46.110(d)]

NO

Could identification of subjects put them at risk of criminal or civil liability, or be socially or economically damaging [Paragraph (C) of Categories.]

YES

Are measures in place to make risks no more than minimal?

YES

Review by convened IRB is required.

NO

Go to Chart 9

NO

Does the research involve a minor change in approved research during the (one year or less) period of approval? [45 CFR 46.110(b)(2)]

NO

Does the review involve a continuing review? [45 CFR 46.109(d)]

NO

Go to Chart 9

YES

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Appendix 5: May informed consent be waived or consent elements be altered under 45 CFR 46.116(d)?

**(Note: If subjects include children to whom 45 CFR part 46, subpart D applies, an alternative provision for waiver of parental permission might apply. [See 45 CFR 46.408(c)])**

From Chart 8 or 9

Will the research or demonstration project be conducted by or subject to the approval of state or local government officials? [45 CFR 46.116(c)(1)]

*YES*

Is the project designed to study, evaluate, or otherwise examine: (i) public benefit of service programs; (ii) procedures for obtaining benefits or services under those programs; (iii) possible changes in or alternatives to those programs or procedures; or (iv) possible changes in methods or levels of payment for benefits or services under those programs? [45 CFR 46.116(c)(1)]

NO

Will the research involve greater than minimal risk, as defined in Section 46.102(i)? [45 CFR 46.116(d)(1)]

*NO*

Is it practicable to conduct the research without the waiver or alteration? [45 CFR 46.116(d)(3)]

YES

No waiver of informed consent or alteration of consent elements is allowed.*

NO

Will waiving or altering the informed consent adversely affect the subjects' rights and welfare? [45 CFR 46.116(d)(2)]

*YES*

Is it practicable to conduct the research without the waiver or alteration? [45 CFR 46.116(c)(2)]

NO

Go to Chart 11

NO

Will pertinent information be provided to subjects later, if appropriate? [45 CFR 46.116(d)(4)]

*YES*

Waiver of informed consent or alteration of consent elements is allowed if IRB documents these findings and approves waiver or alteration.

*NO*

If informed consent is not waived entirely

*Note: See OHRP guidance on informed consent requirements in emergency research at http://www.hhs.gov/ohrp/regulations-and-policy/guidance/emergency-research-informed-consent-requirements/index.html for further information on emergency research informed consent waiver.*

Appendix 6: May documentation of informed consent be waived under 45 CFR 46.117(c)?

From Chart 10

Would the consent document be the only record linking the subject and the research and would the principal risk be potential harm resulting from a breach of confidentiality? [45 CFR 46.117(c)(1)]

NO

Does the research present no more than minimal risk and involve no procedures for which written consent is normally required outside the research context? [45 CFR 46.117(c)(2)]

YES

IRB may waive the requirement for a signed consent form for some or all subjects.

NO

IRB may require investigator to provide subjects with a written statement regarding the research. [45 CFR 46.117(c)]

YES

If IRB Allows Waiver of Documentation Under 45 CFR 46.117(c)(1)

Investigator will ask each subject if he or she wants documentation linking the subject with the research. [45 CFR 46.117(c)(1)]

Subject’s wishes will govern whether informed consent is documented. [45 CFR 46.117(c)(1)]

END

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