# On the use of clinically accepted black-box systems for EEG seizure prediction

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**We hope this interactive presentation provides a more intuitive understanding of the obtained social network while allowing free exploration of the ecosystem. Here you will find:**

**i) a seizure prediction process, from pre-surgical monitoring acquisition until prospective application development (from slides 2 to 18);**

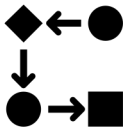
**ii) the seizure prediction ecosystem and guidelines that you can freely explore (from slides 19 to 104);**

**iii) the discussion of our ecosystem, guidelines, and explainability conclusions (from slides 105 to 108).**

**i) how to navigate in this presentation, how to find, and cite this paper (slide 109);**

**To end this presentation,**
**press escape button at any moment.**

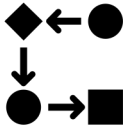
**Product Process**

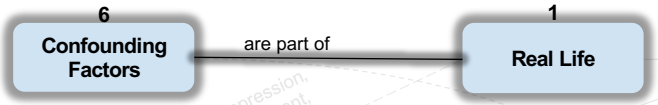


**Here you can see a straightforward product process of seizure prediction device, from pre-surgical monitoring to a clinical trial.**

**Begin**

Product Process






1. We begin with a Drug-Resistant Epilepsy (DRE) patient.

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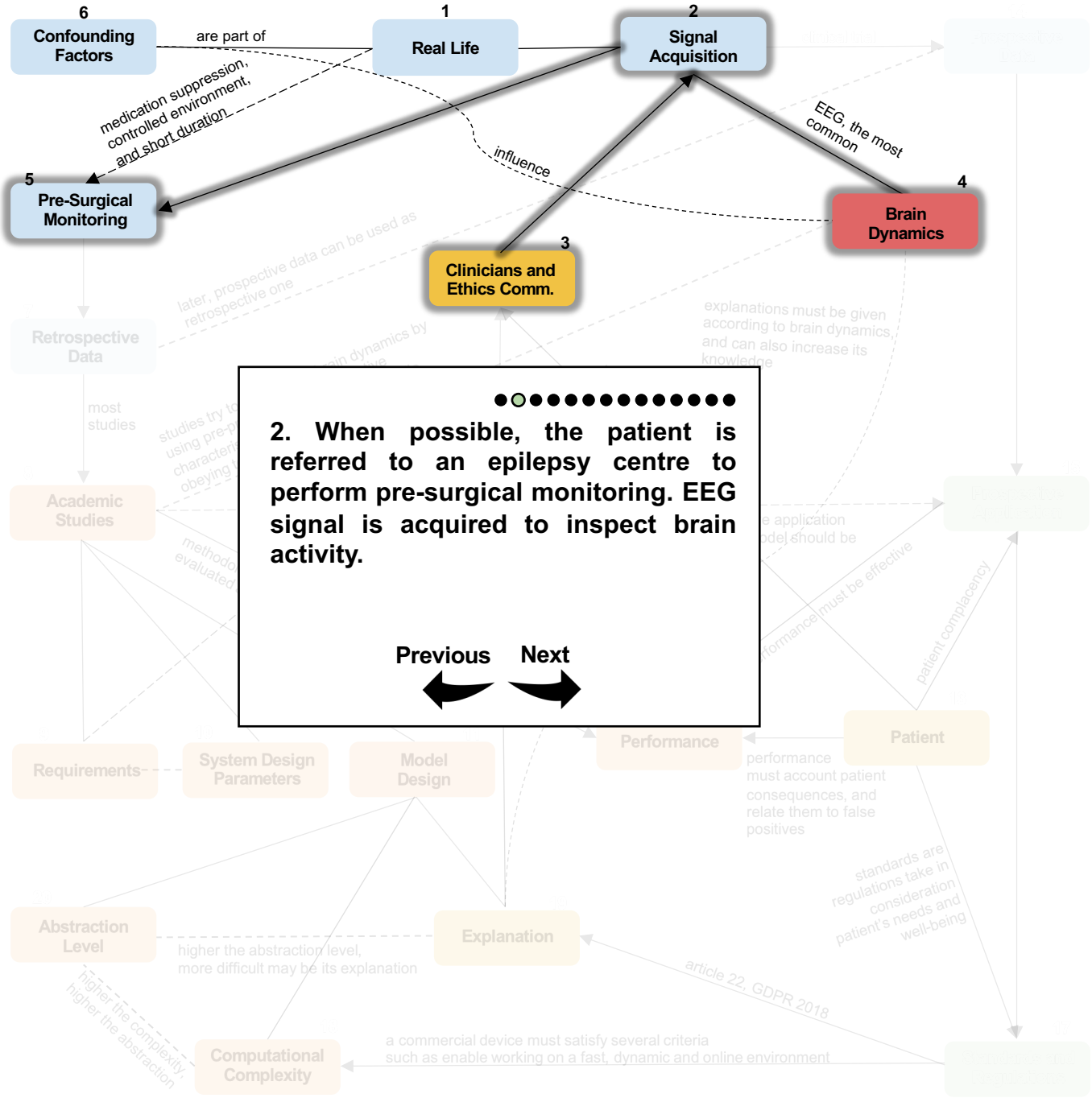


Product Process

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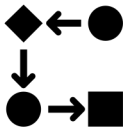

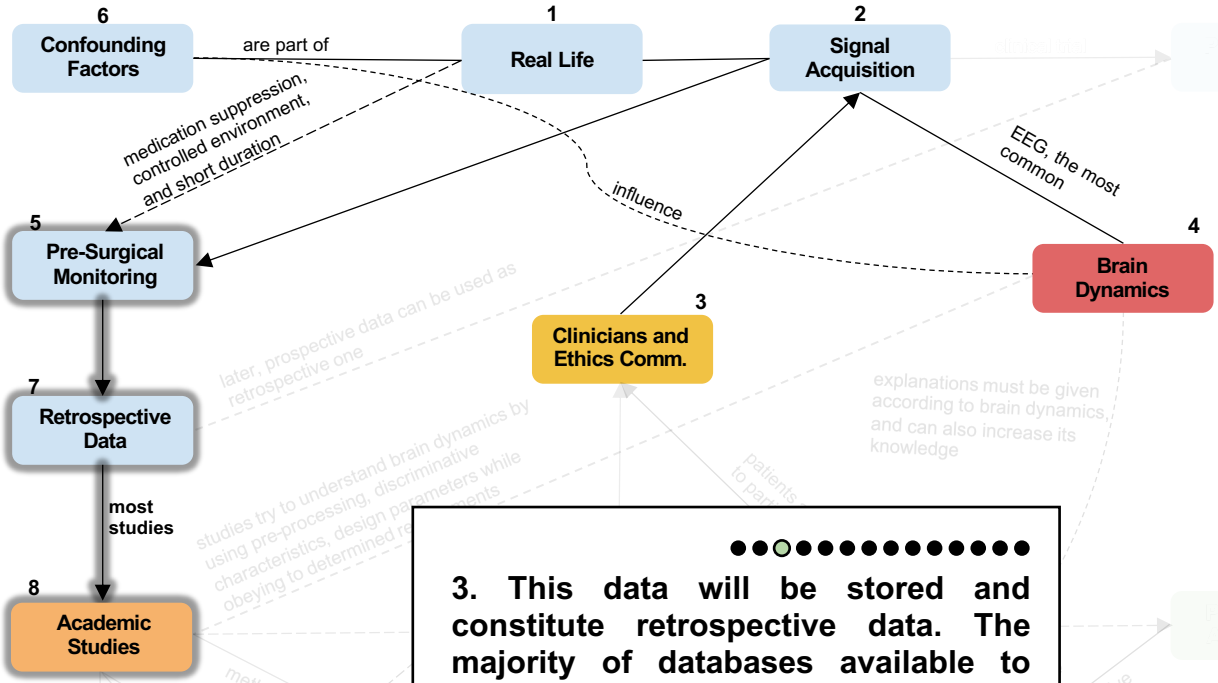


3. This data will be stored and constitute retrospective data. The majority of databases available to perform academic studies concerns pre-surgical monitoring conditions.

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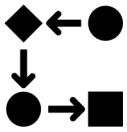
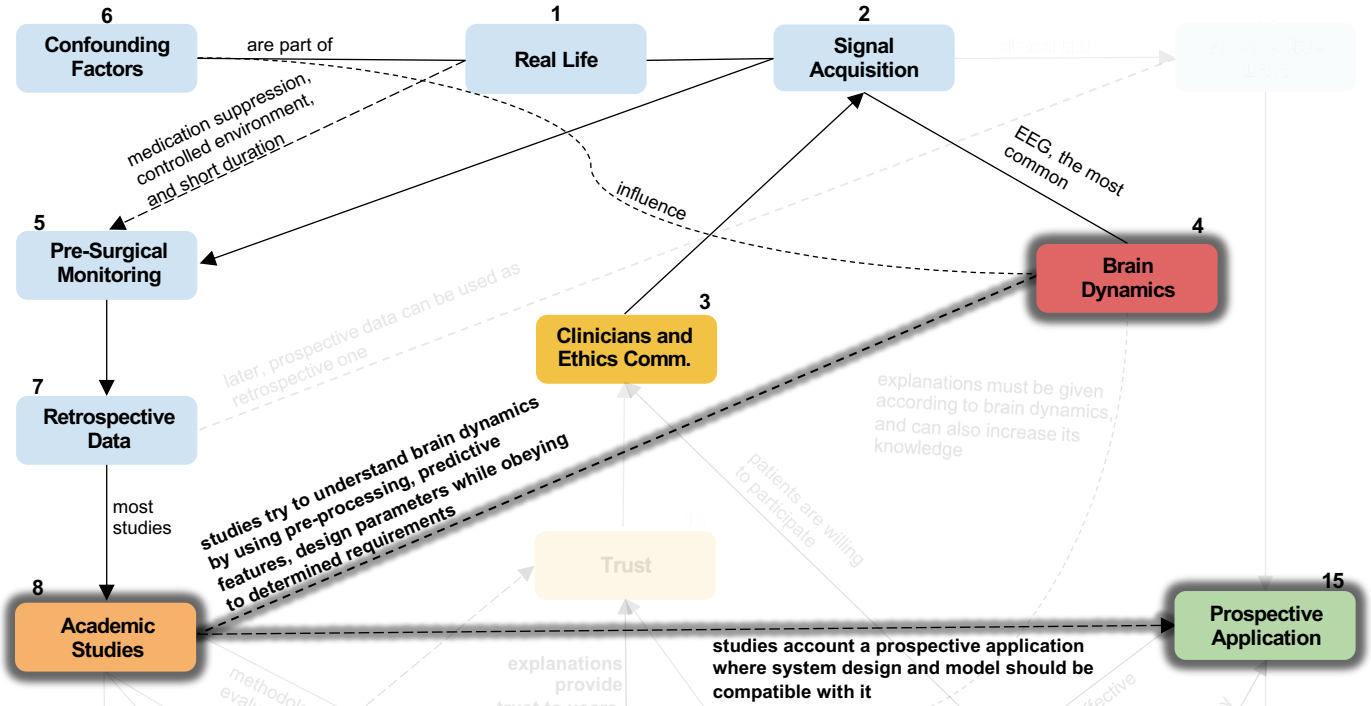
Product Process






4. Studies try to capture and understand brain dynamics with the goal of predicting seizures. These studies must envision a real-application scenario.

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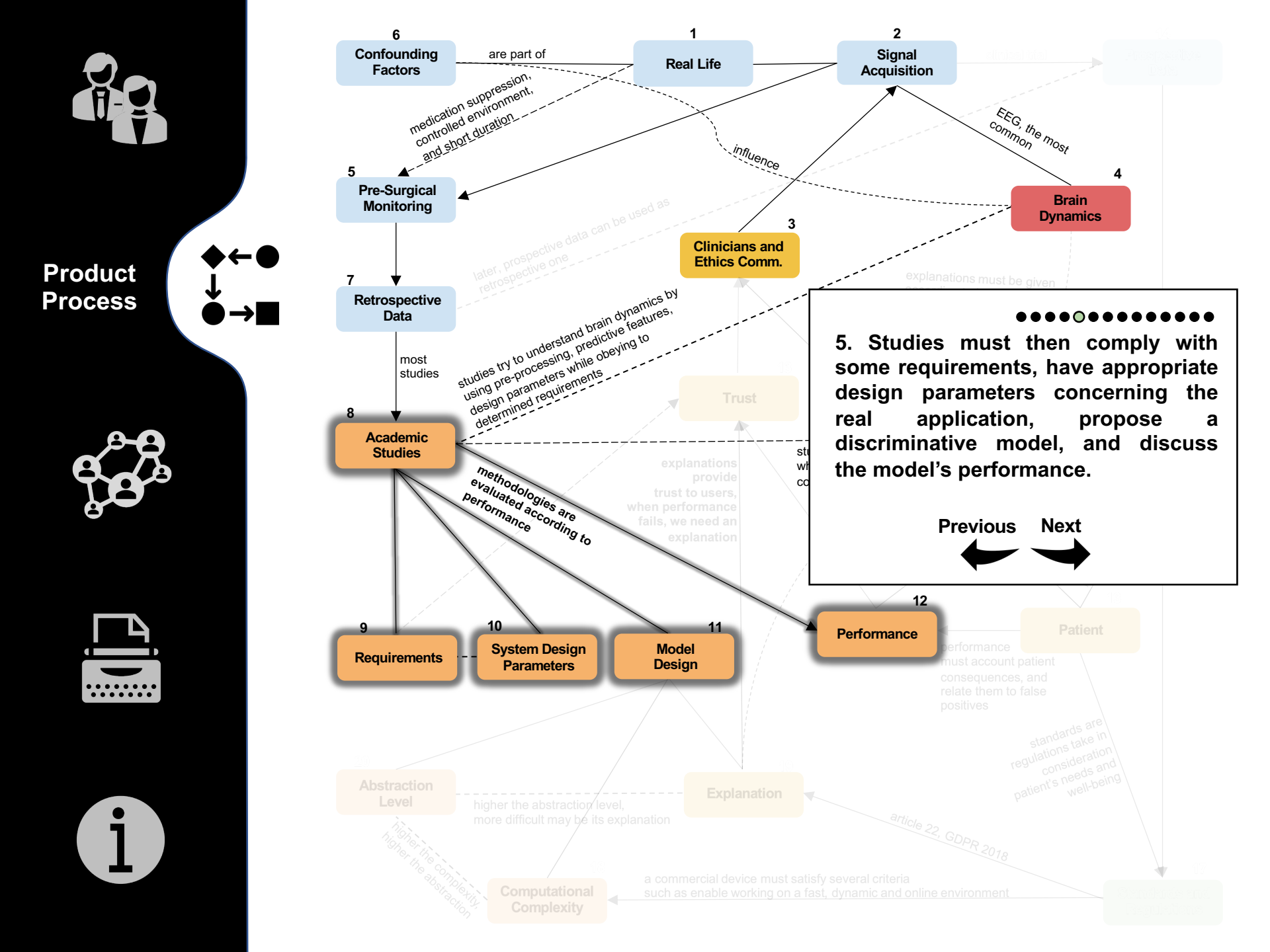
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methodologies are evaluated according to performance
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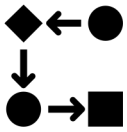
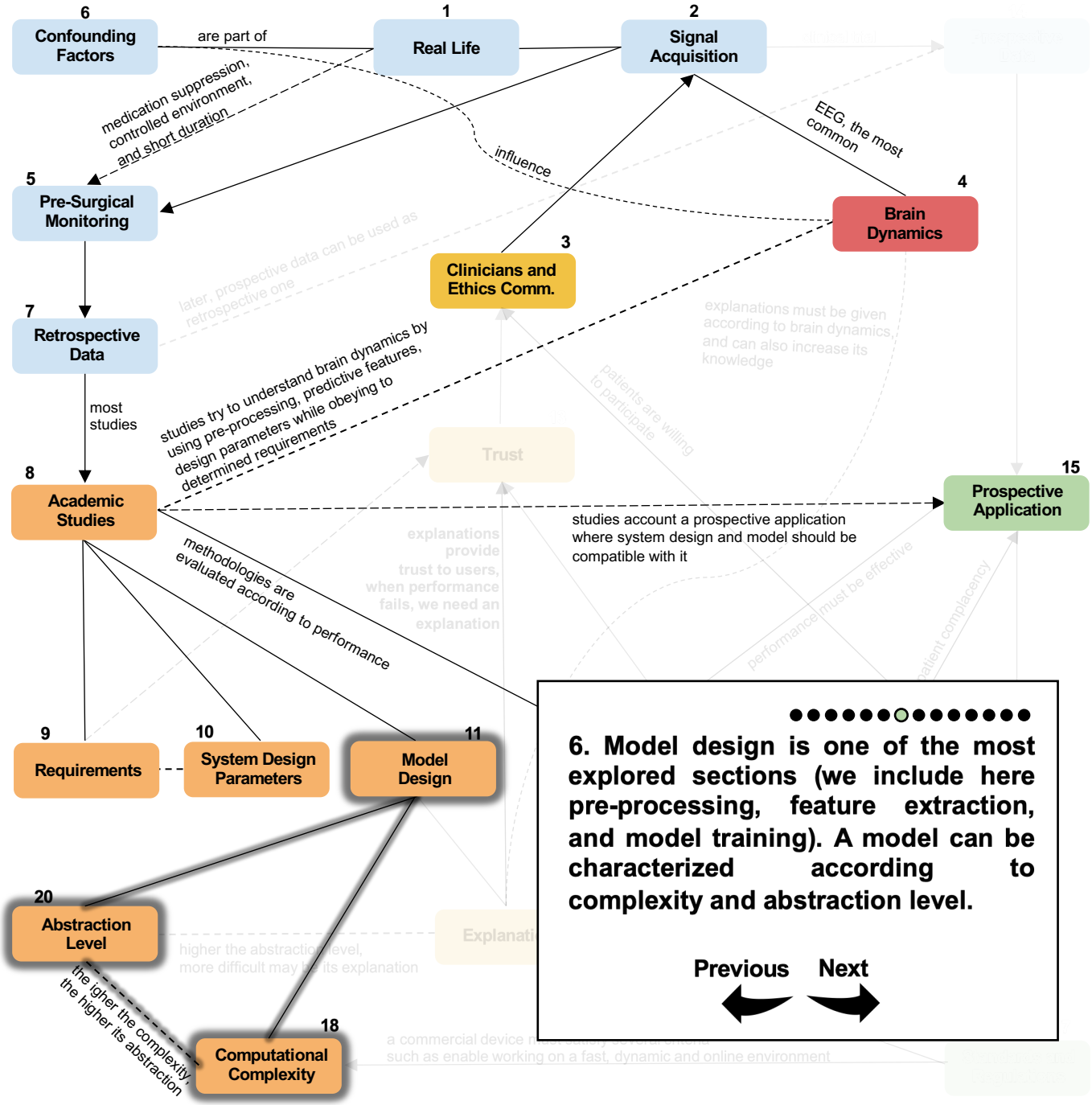
5. Studies must then comply with some requirements, have appropriate design parameters concerning the real application, propose a discriminative model, and discuss the model's performance.
Previous
Next

Product Process






**6. Model design is one of the most explored sections (we include here pre-processing, feature extraction, and model training). A model can be characterized according to complexity and abstraction level.**

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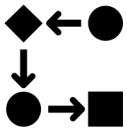

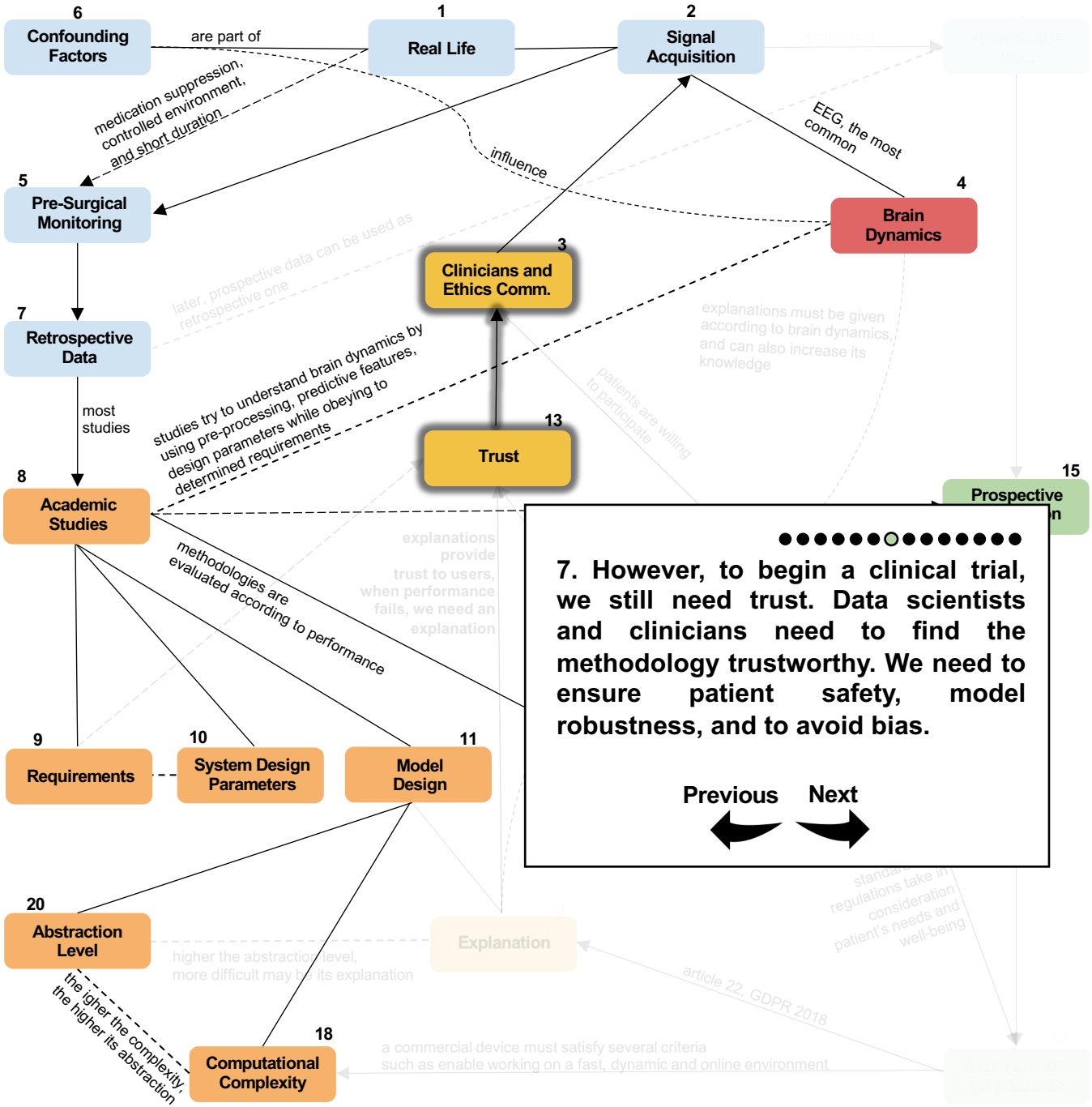


**7. However, to begin a clinical trial, we still need trust. Data scientists and clinicians need to find the methodology trustworthy. We need to ensure patient safety, model robustness, and to avoid bias.**

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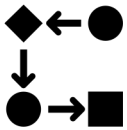

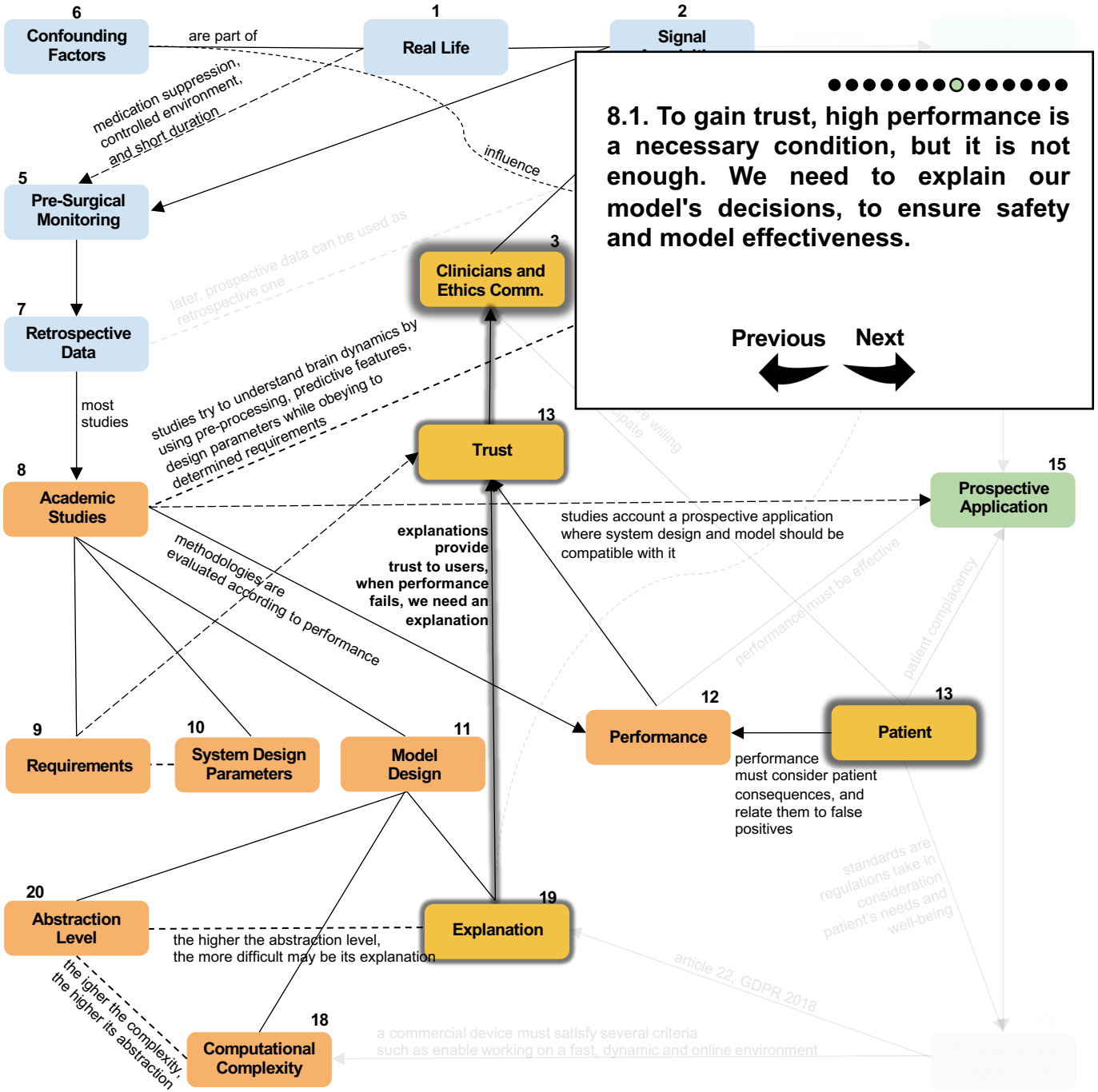


**8.1. To gain trust, high performance is a necessary condition, but it is not enough. We need to explain our model's decisions, to ensure safety and model effectiveness.**

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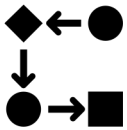

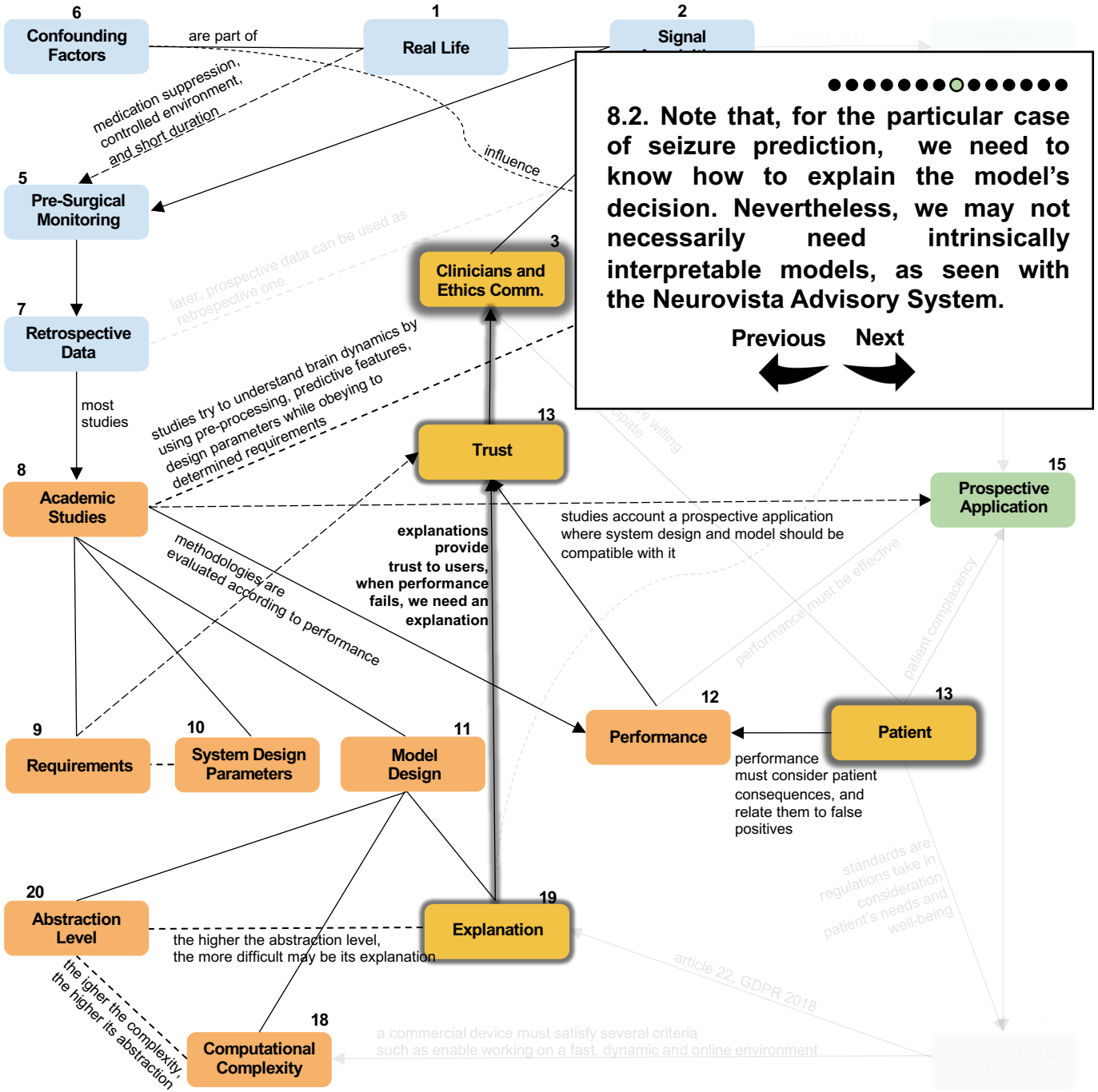


**8.2. Note that, for the particular case of seizure prediction, we need to know how to explain the model's decision. Nevertheless, we may not necessarily need intrinsically interpretable models, as seen with the Neurovista Advisory System.**

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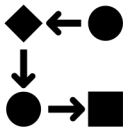

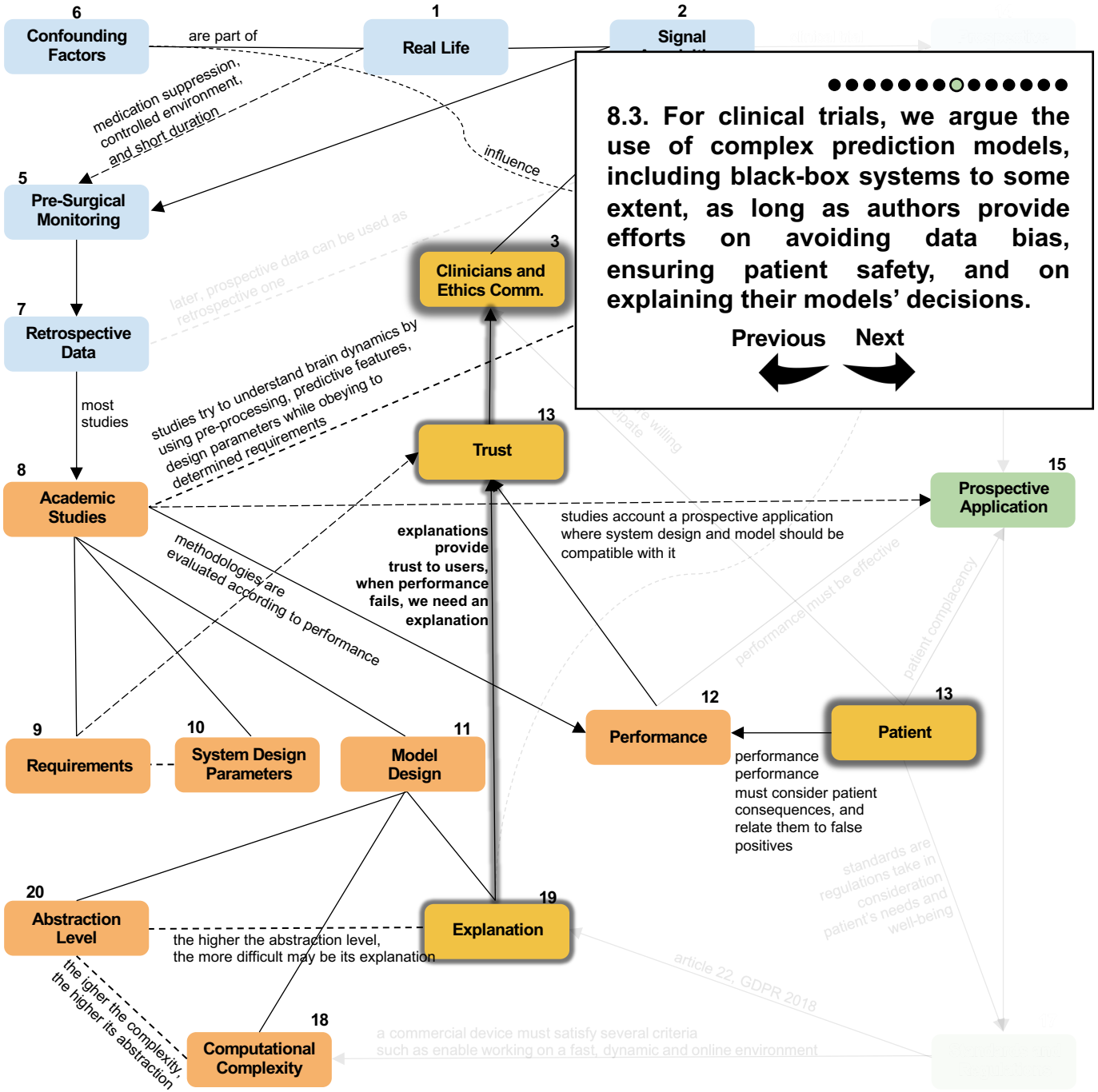


**8.3. For clinical trials, we argue the use of complex prediction models, including black-box systems to some extent, as long as authors provide efforts on avoiding data bias, ensuring patient safety, and on explaining their models' decisions.**

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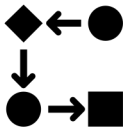

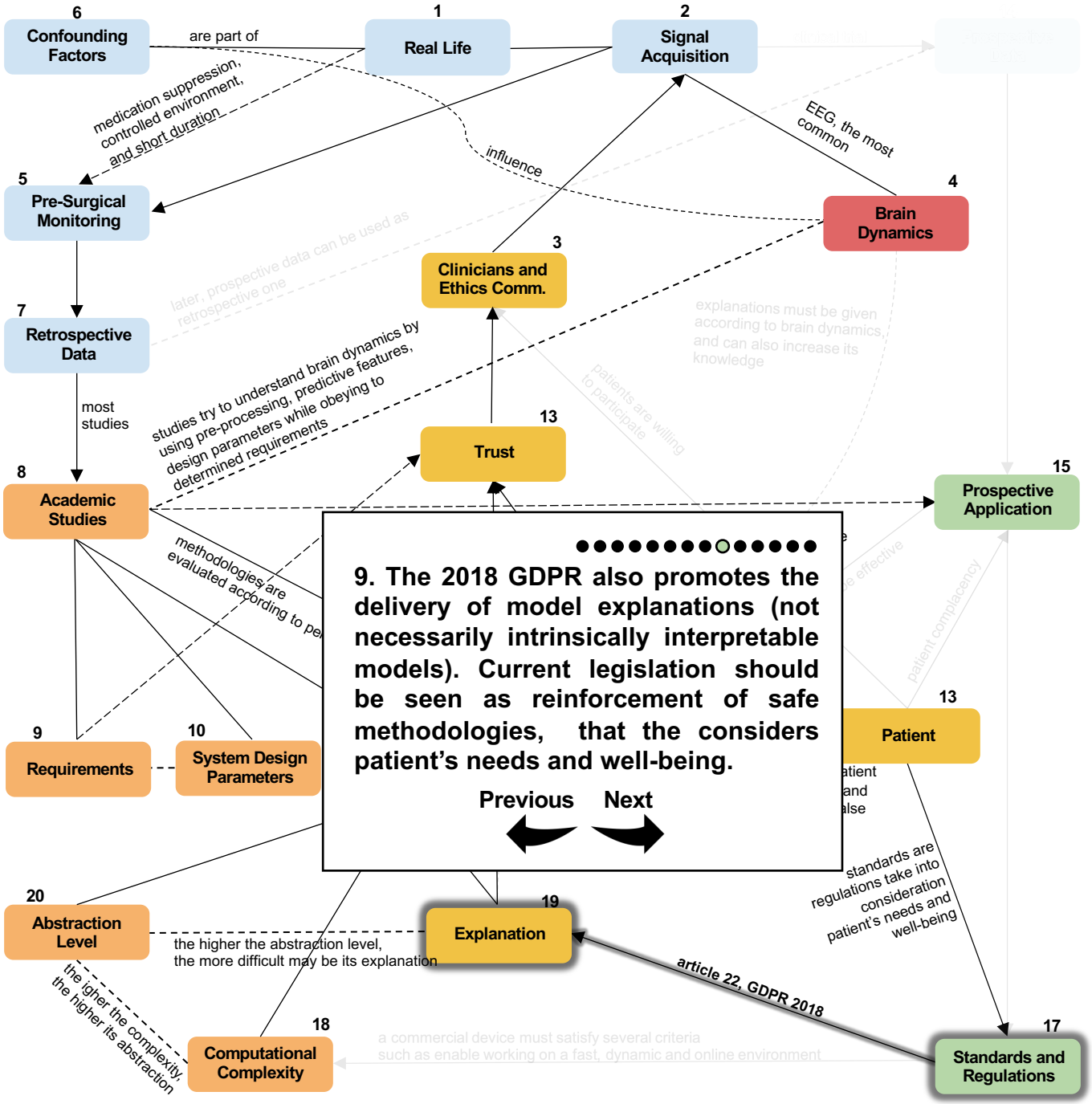

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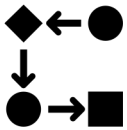

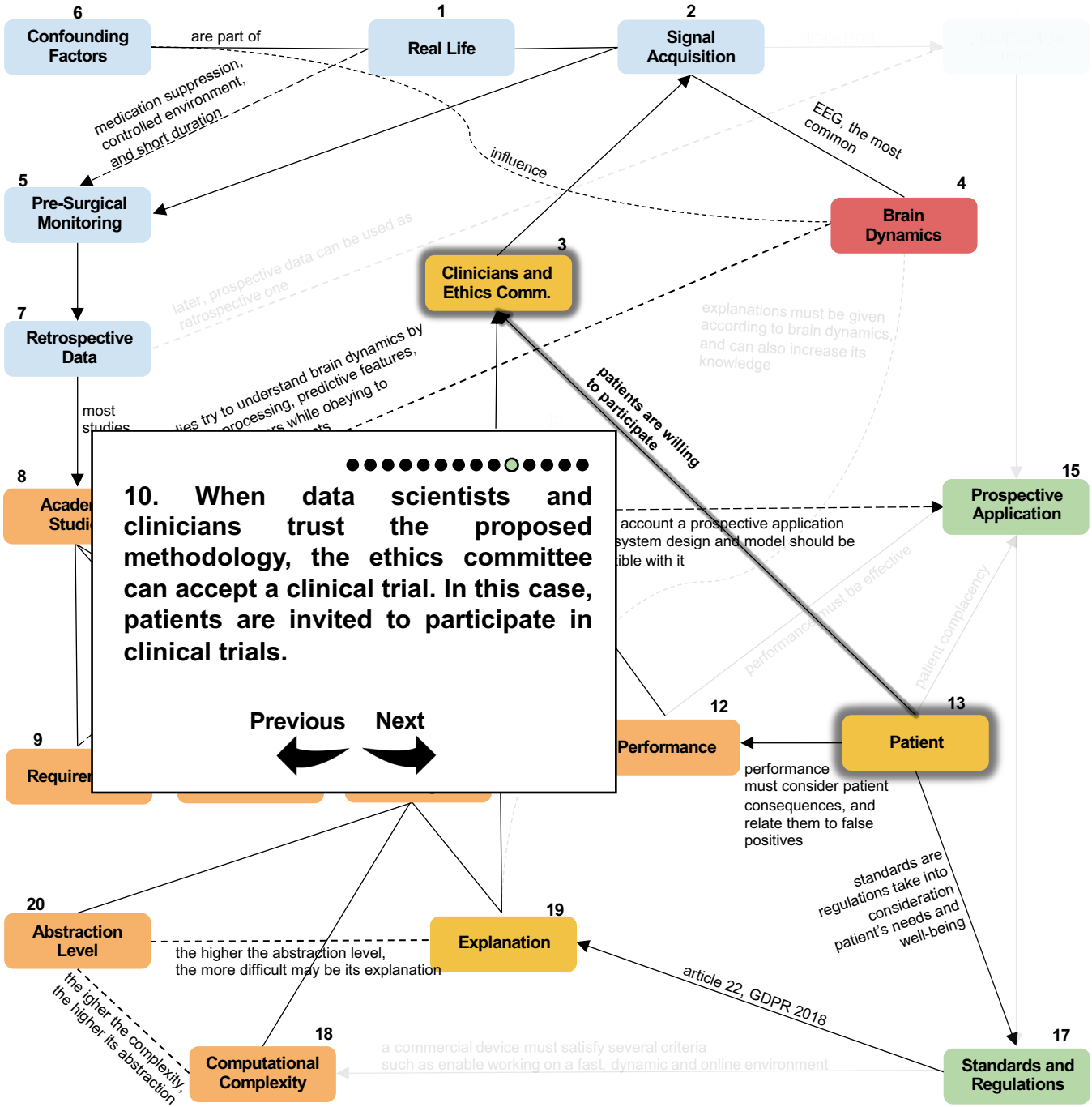


**10. When data scientists and clinicians trust the proposed methodology, the ethics committee can accept a clinical trial. In this case, patients are invited to participate in clinical trials.**

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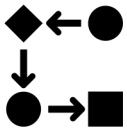

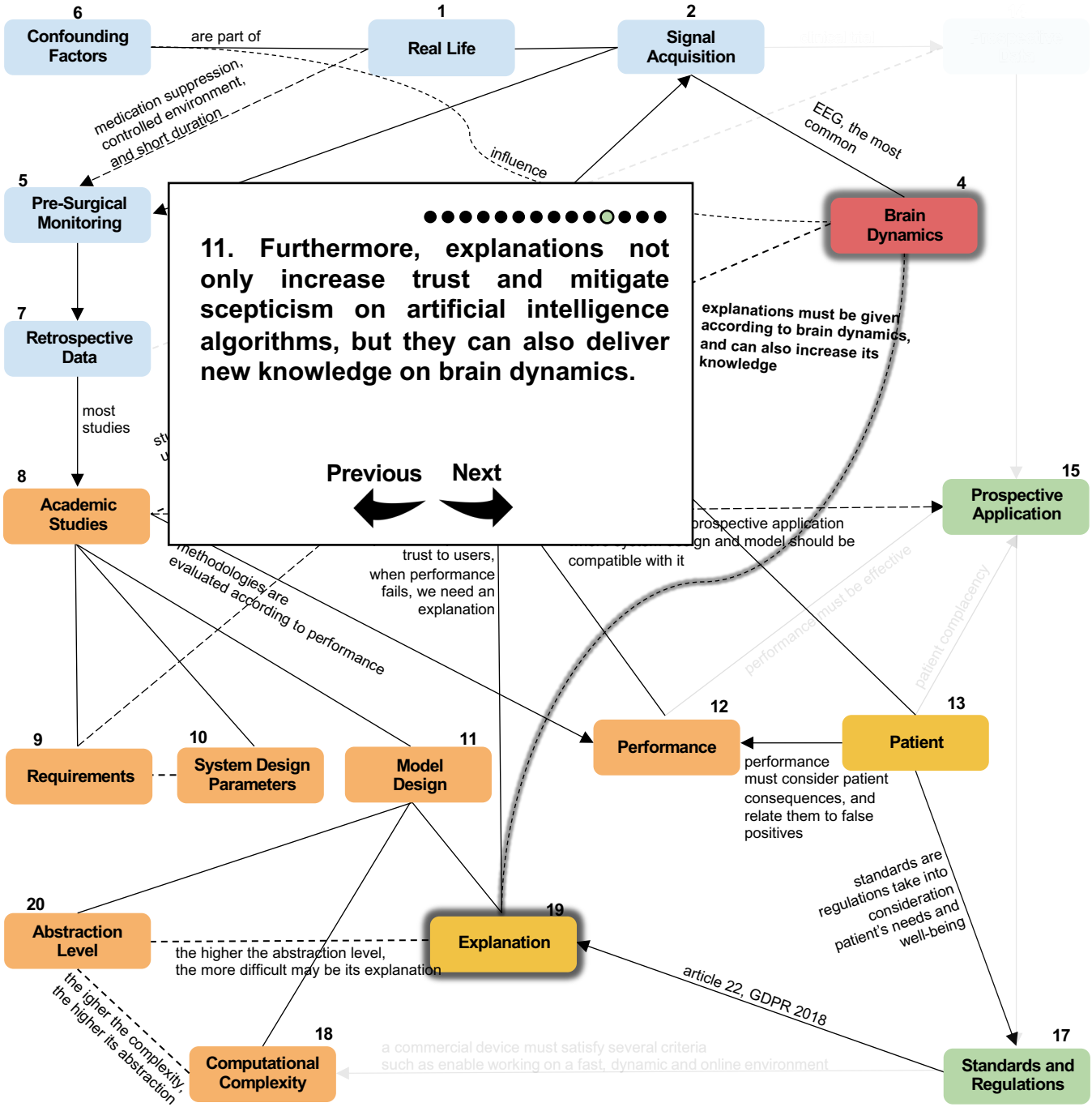

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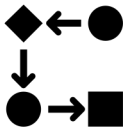

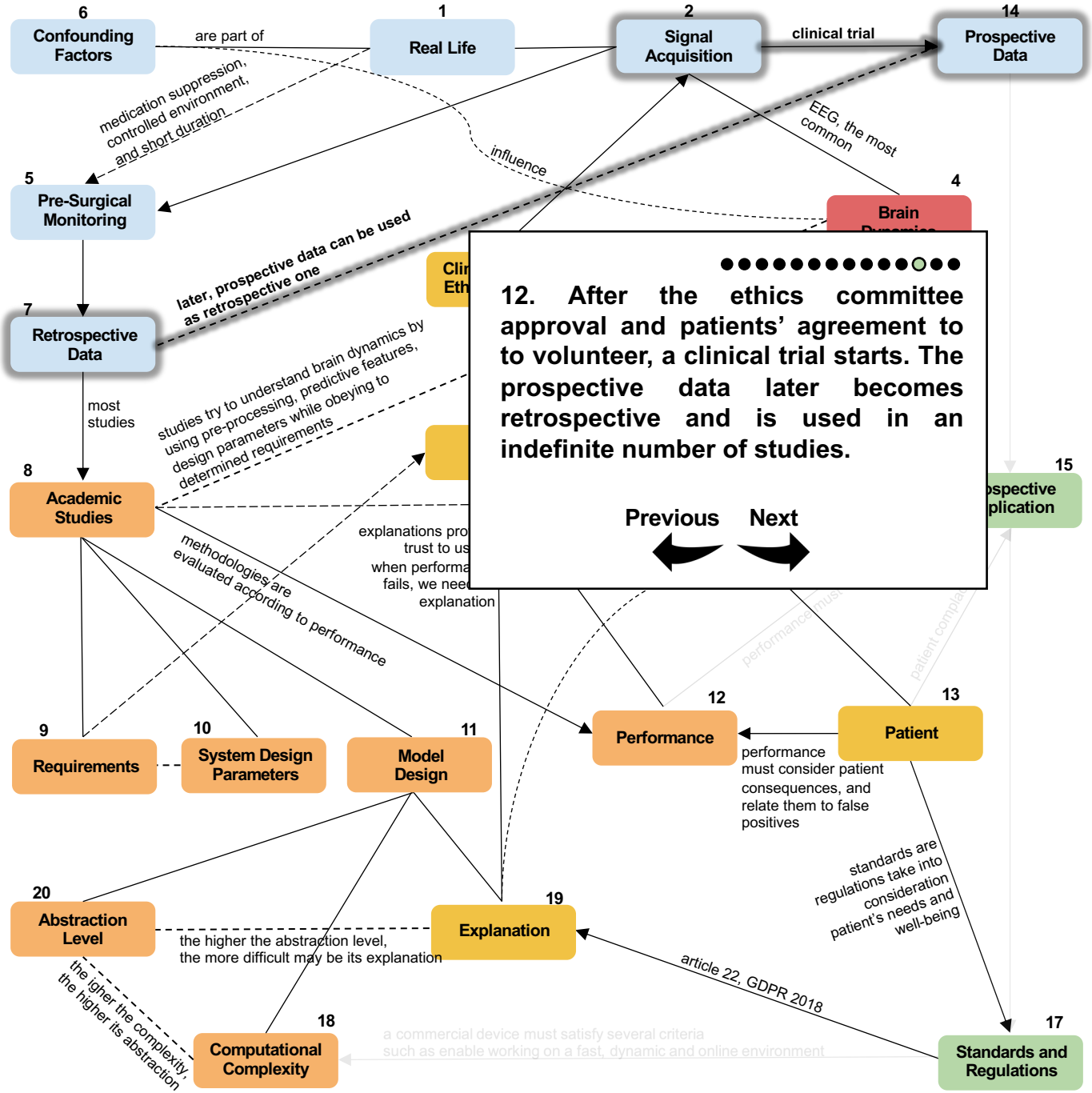

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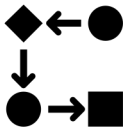

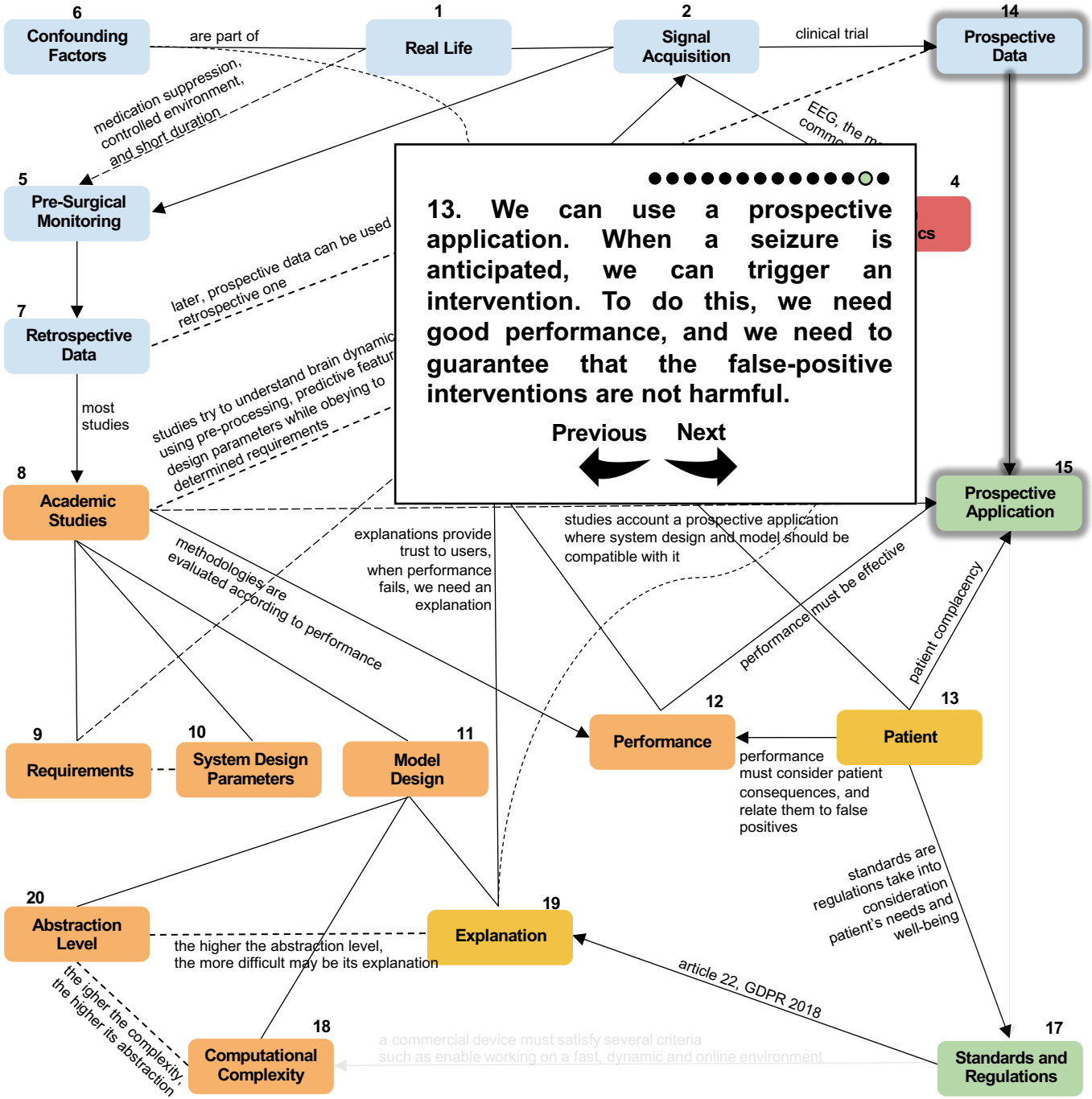

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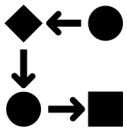
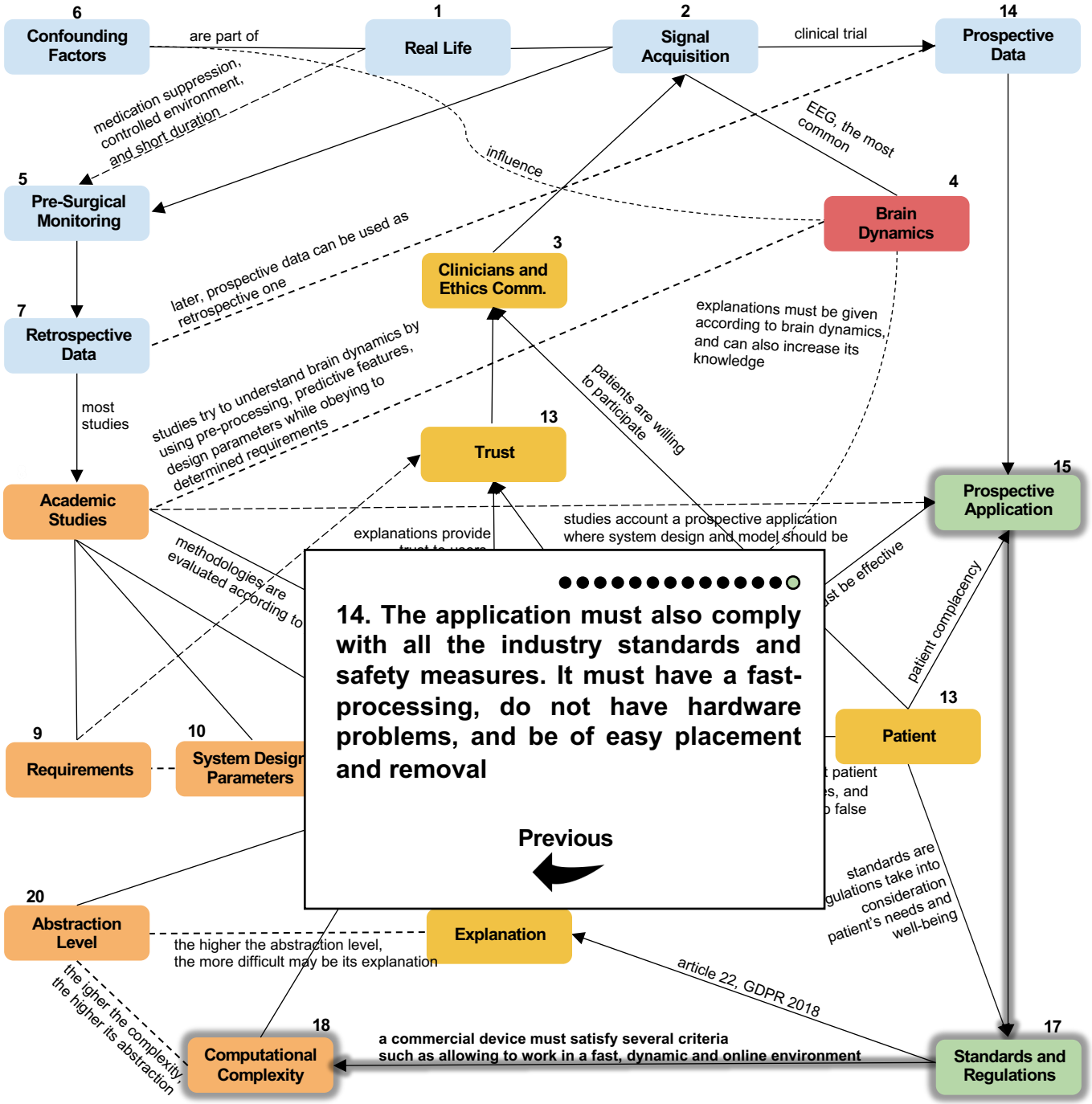
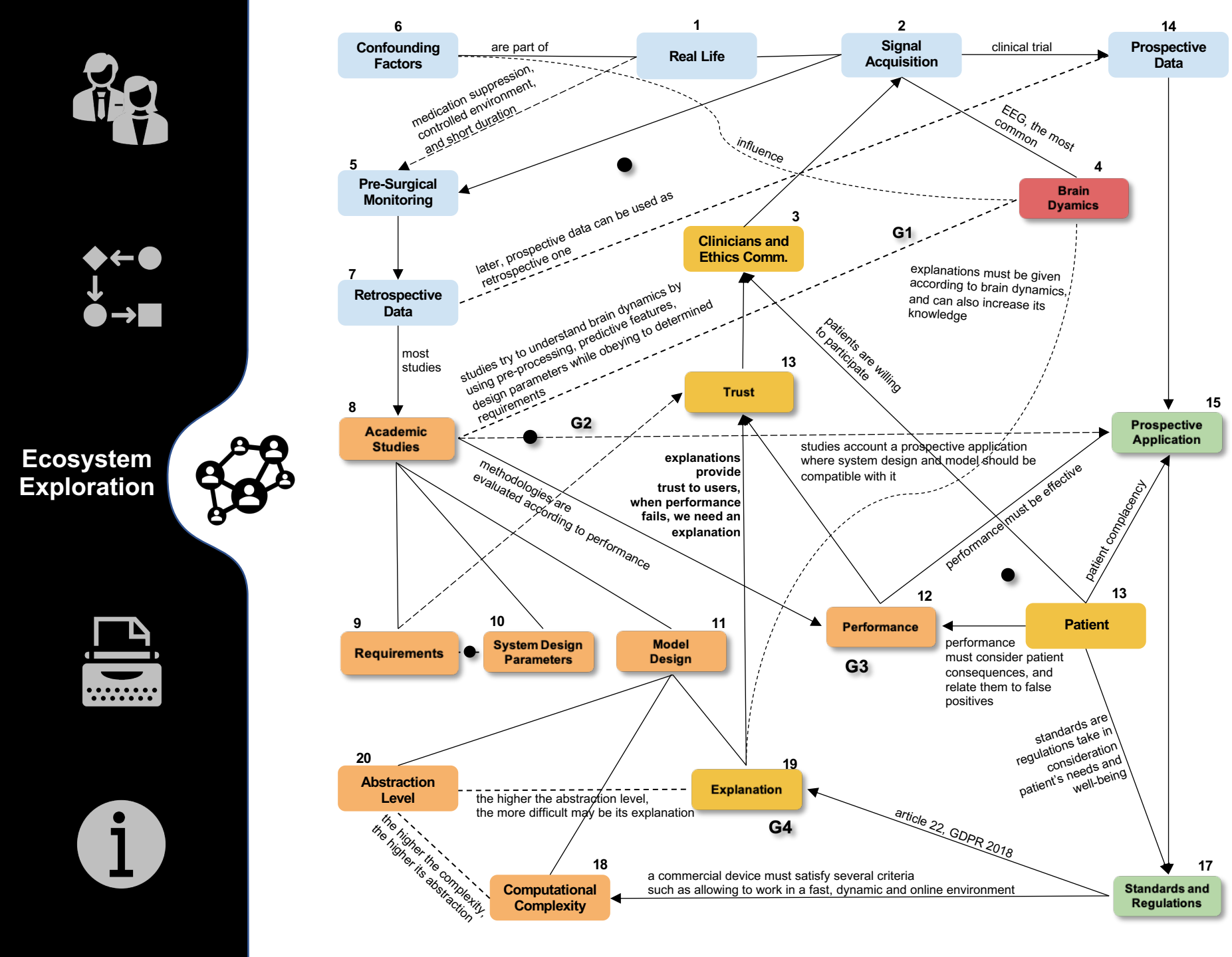





Ecosystem Exploration
Here you can explore the ecosystem, see the performed encapsulations, and verify where our Guidelines can be placed in it.
Begin
Confounding Factors
are part of
medication suppression, controlled environment, and short duration
influence
Pre-Surgical Monitoring
later, prospective data can be used as retrospective one
Retrospective Data
most studies
Academic Studies
Brain Dynamics
Clinicians and Ethics Comm.
explanations must be given according to brain dynamics, and can also increase its knowledge
patient complacency
Patient
performance must account patient consequences, and relate them to false positives
Performance
Requirements
System Design Parameters
Model Design
Abstraction Level
higher the abstraction level, more difficult may be its explanation
Explanation
standards are regulations take in consideration patient's needs and well-being
article 22, GDPR 2018
higher the complexity, higher the abstraction
Computational Complexity
a commercial device must satisfy several criteria such as enable working on a fast, dynamic and online environment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patients are willing to participate
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Trust
8
Academic Studies
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Prospective Application
explanations provide trust to users, when performance fails, we need an explanation
studies account a prospective application where system design and model should be compatible with it
methodologies are evaluated according to performance
performance must be effective
patient complacency
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19
Explanation
the higher the abstraction level, the more difficult may be its explanation
G4
article 22, GDPR 2018
the higher the complexity, the higher its abstraction
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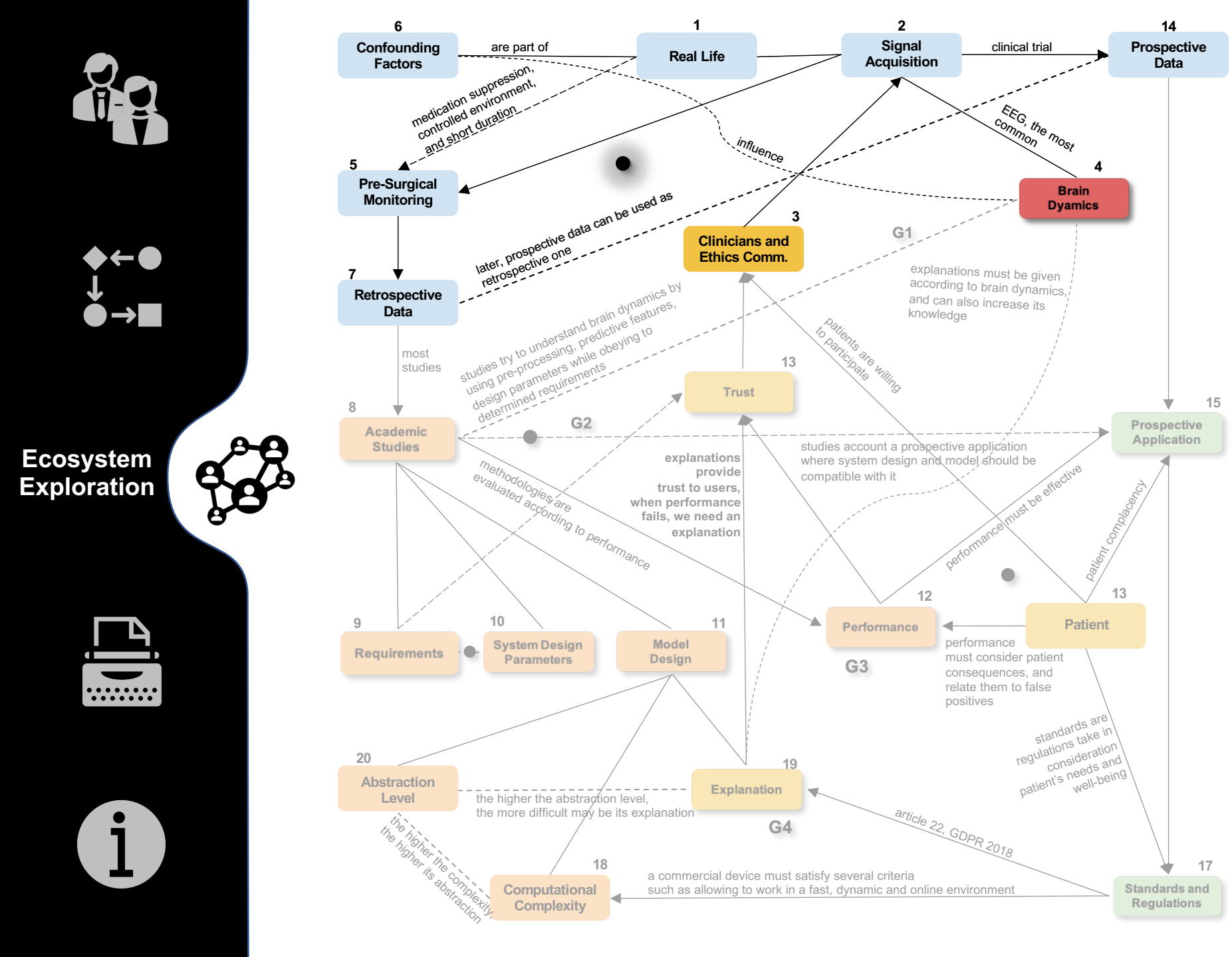
17
Standards and Regulations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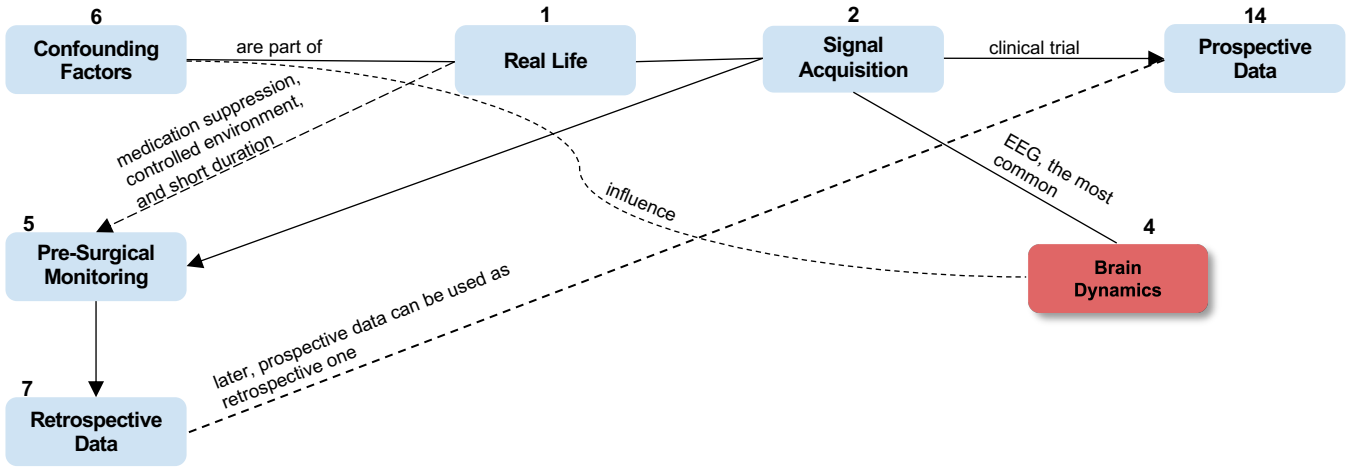
# Real-Life and Pre-Surgical Monitoring

We begin with the real-life of an epileptic patient (1). Years after diagnosed with Drug-Resistant Epilepsy (DRE), a patient is referred to an epilepsy centre to undergo pre-surgical monitoring (5) (this process may not be as frequent as desired, happening for less than 1% of DRE patients). The latter evaluates brain electrical activity (4) to identify the epileptic focus. If easily detected, removing the epileptic region is a possible solution. To perform this evaluation, one must perform signal acquisition (2), being the EEG the most commonly used signal (2--4). To acquire and study this data, we require patient consent (16→3) and an ethical justification (3). In this case, there is a strong motivation.

Most studies are performed using pre-surgical monitoring data. However, it may not represent real-life (2→5): the patient is in a controlled environment; the brain may take time to adapt to the acquisition material (as initial data may need to be discarded); clinicians suppress medication to increase seizure occurrence frequency; and the short period (a couple of weeks) of clinic admission and signal recording may mask the influence (1- -5) of day-to-day confounding factors (6- -4), such as stress, circadian and ultradian rhythms.

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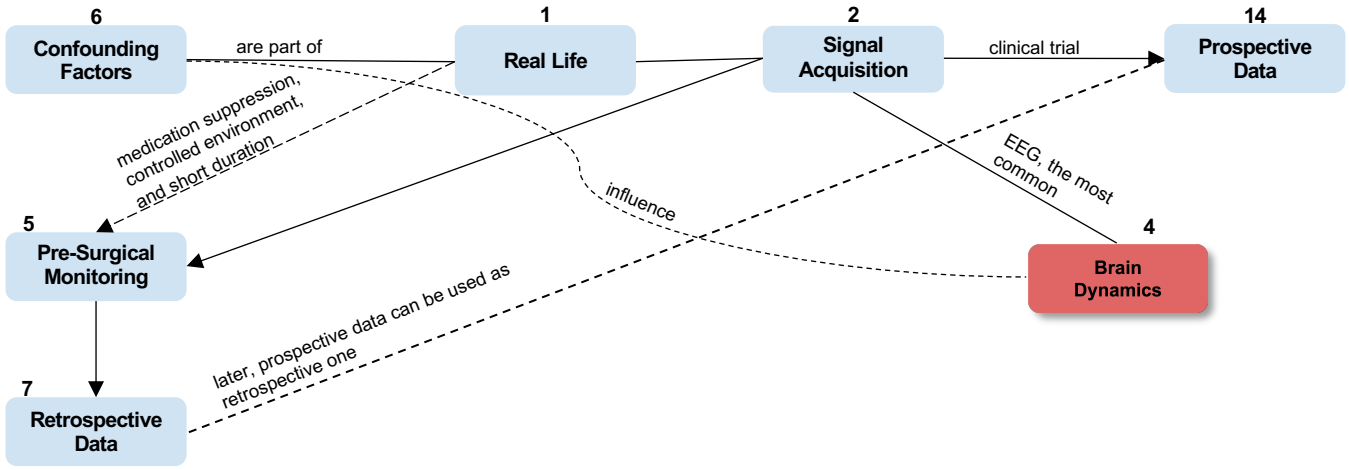
More Info

# Real-Life and Pre-Surgical Monitoring

Most databases comprise pre-surgical monitoring recordings, which correspond to retrospective data (7) that authors can indefinitely use in academic studies (8). To collect prospective data during a clinical trial in a real-life scenario (2→14), it is also necessary to find sufficiently strong and ethical motivation, which we will discuss later. Briefly, prospective studies require a significantly higher patient complacency, involve longer time periods, and demand additional resources. Prospective data then becomes retrospective (14- -7).

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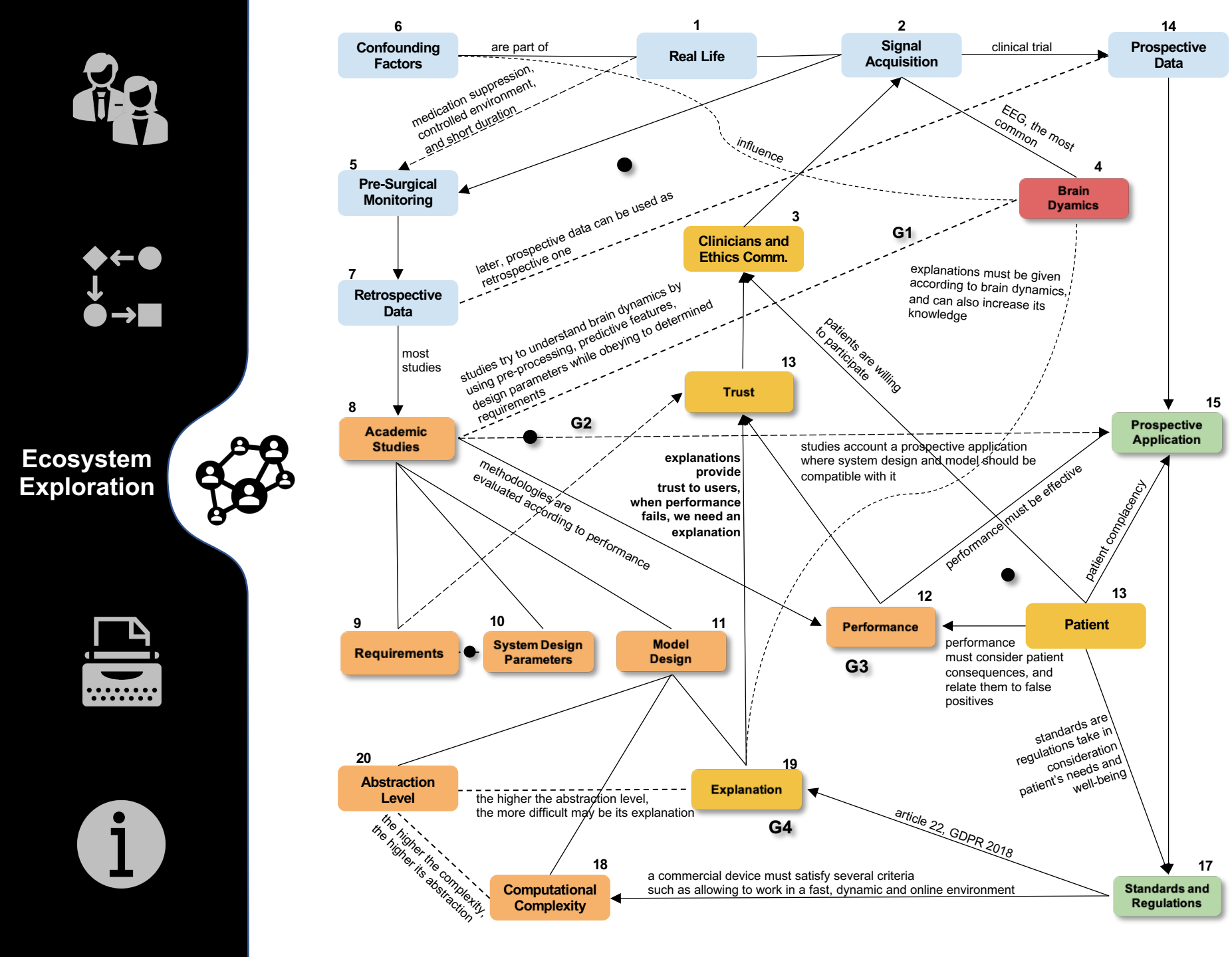
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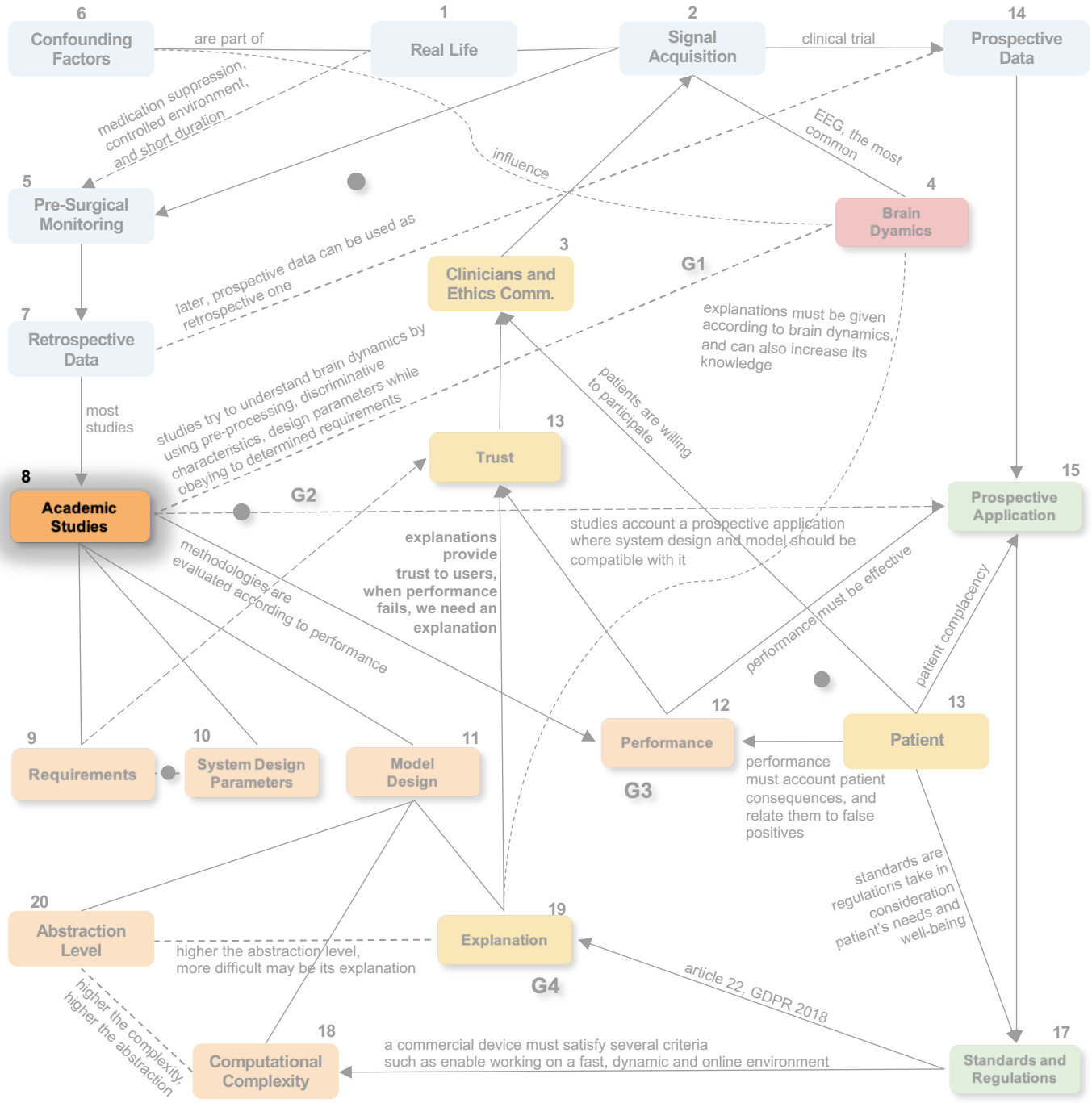
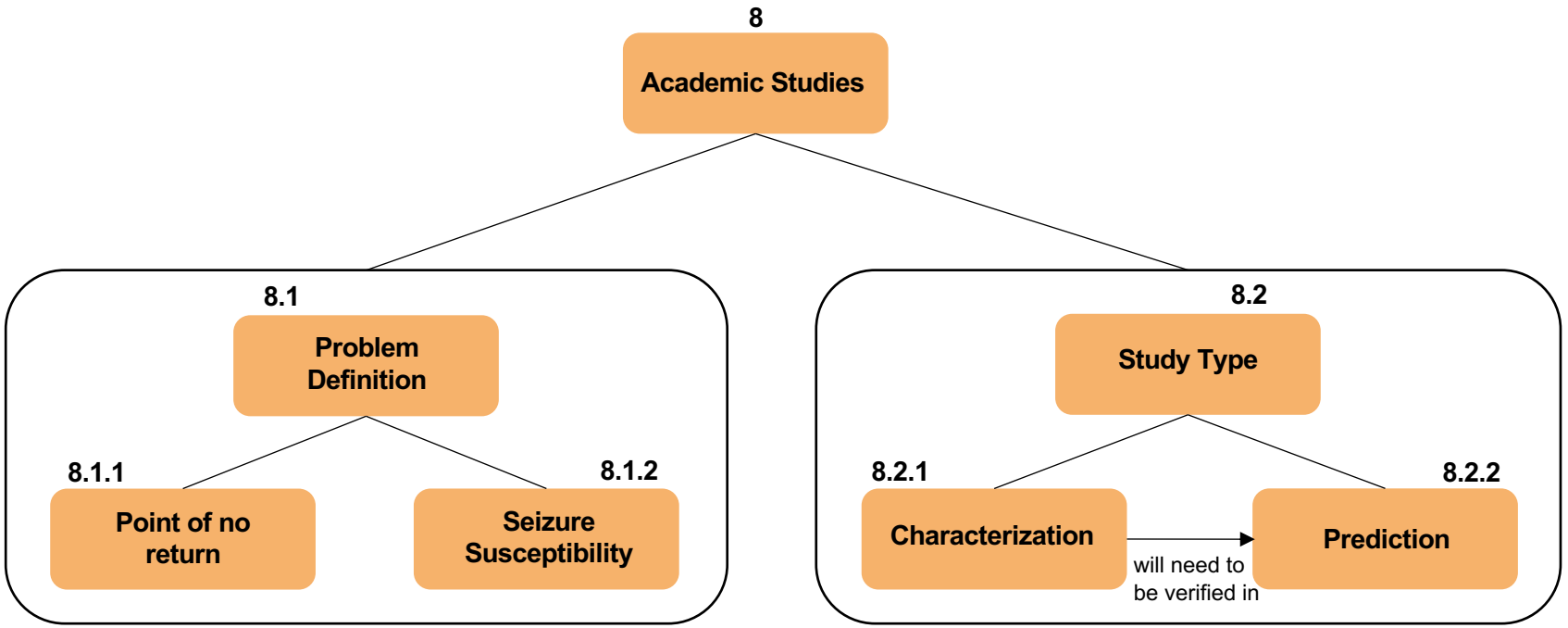
## Ecosystem Exploration



# Encapsulation of Academic Studies

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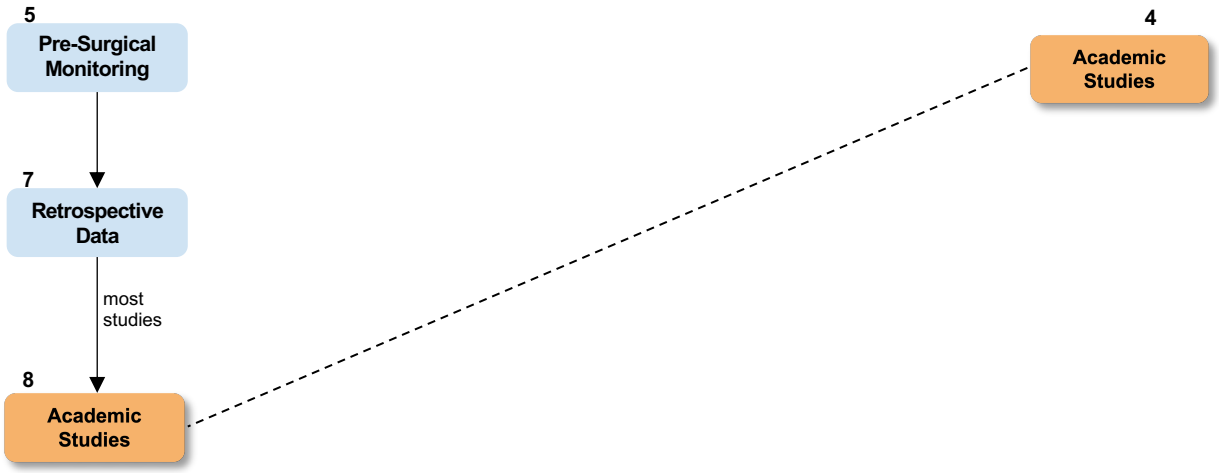
# Academic Studies

Academic studies attempt to discover relevant brain dynamics by, under some requirements, finding optimal signal processing strategies, predictive features, and accurate models (8- -4). The majority uses retrospective data because of its availability. In such cases, findings should be interpreted as a proof of concept to demonstrate that some methodologies may be more suitable, even though they still need to be tested in a real context.

Inevitably, we make several assumptions (see "Assumptions" section in Supplementary Material for more information) when we design a new study. These may result from the used mathematical models, available data and other limitations, or even reflect the researcher knowledge concerning brain dynamics (8- 4).

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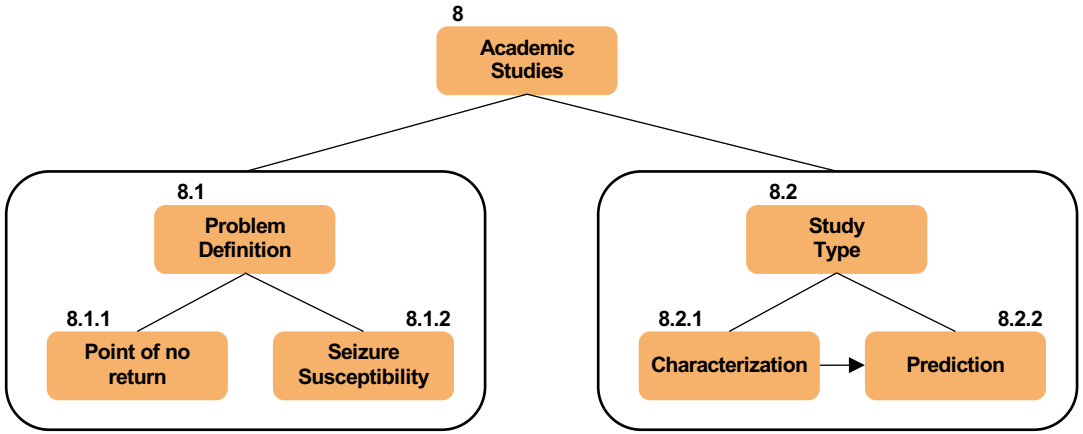
# Academic Studies

Authors attempt to predict seizures by assuming the existence of the pre-ictal period. The latter is the transition between the normal brain state (inter-ictal period) and a seizure (ictal period). We can define the pre-ictal period in two different ways (8.1). One approach assumes it as a point of no return (8.1.1), leading necessarily to a seizure. Another method is to envision it as a period of brain susceptibility (8.1.2) where a hyperexcitable state may not lead to a seizure. These hypothesis influence significantly the experimental design, as it may be more difficult to have a ground truth or, in other words, a correct labelling on brain hyperexcitability when no seizure occurred. Thus, despite limiting the understanding of brain dynamics, the point of no return is commonly used.

It is relevant to note the existence of two types of study (8.2): characterization (8.2.1) and prediction (8.2.2). In the first, authors try to find predictive models and/or predictive features that capture a clear distinct behaviour between a normal brain state and the pre-ictal period. However, the prediction potential of these should be further evaluated by integrating this information in a seizure prediction methodology (8.2.1→8.2.2) and observing the obtained performance. Prediction studies are the ones that simulate a real-life scenario and are designed to deliver timely interventions (8- -15). Therefore, these are the most reported in the literature and are the ones we focus here.

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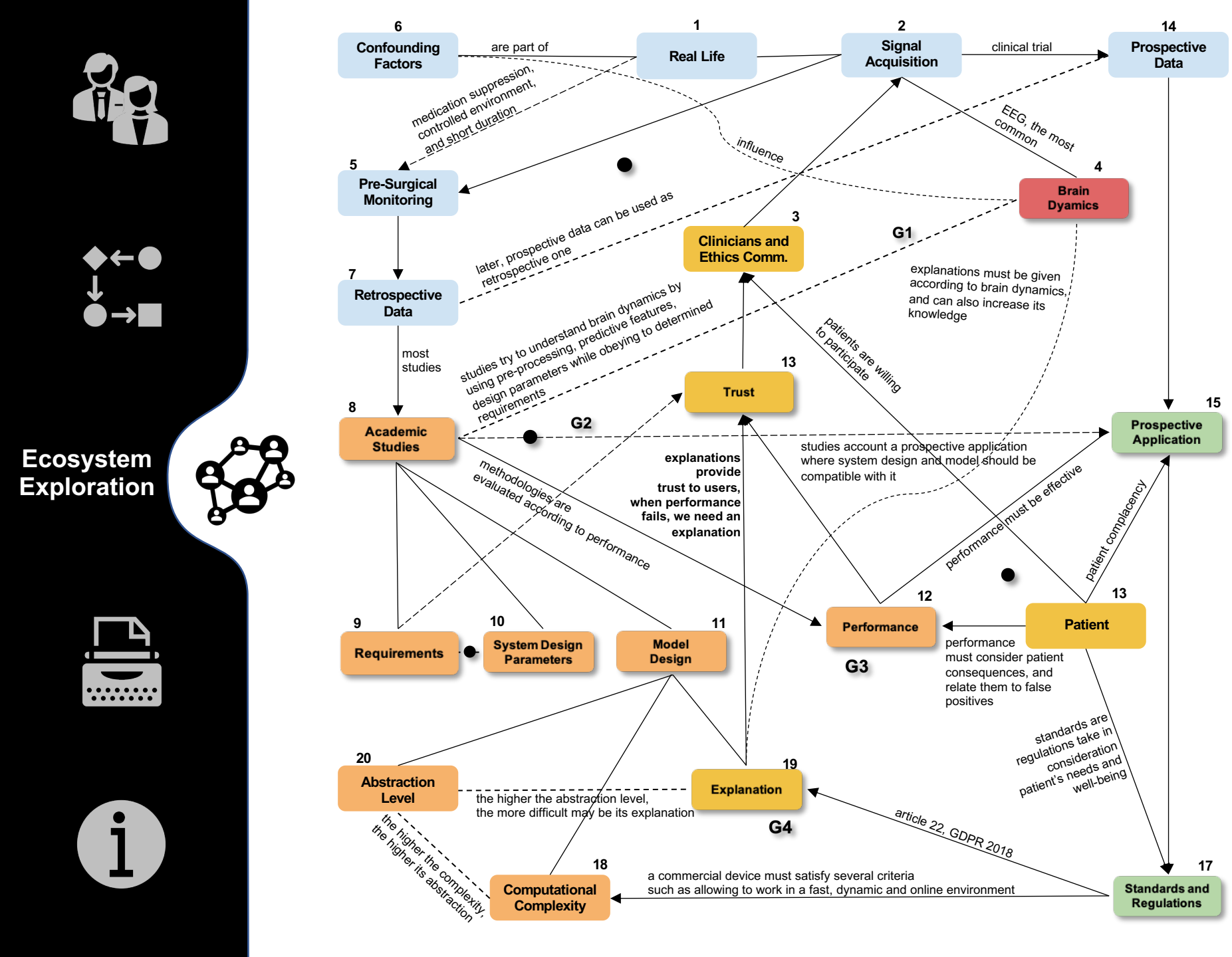
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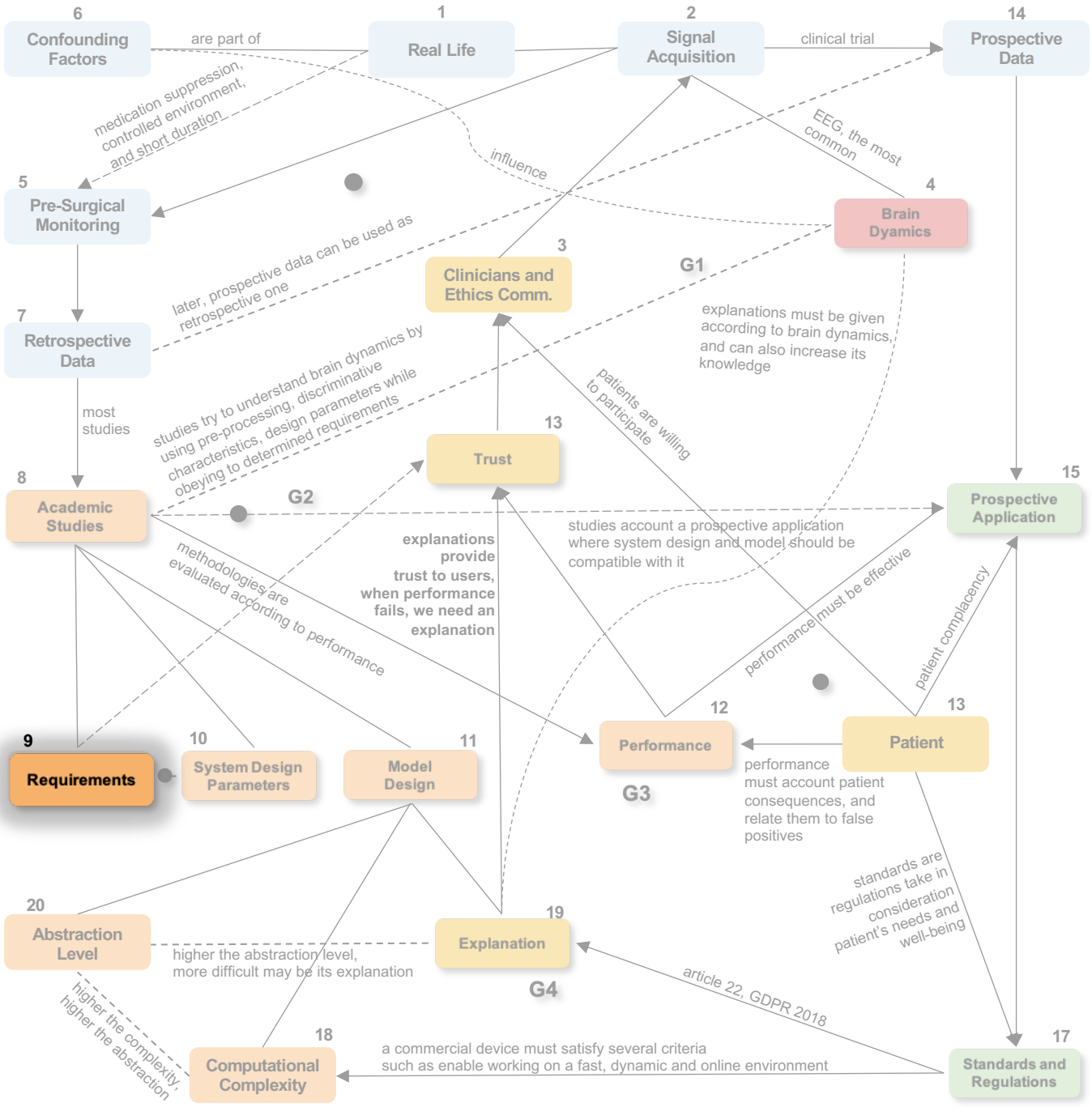
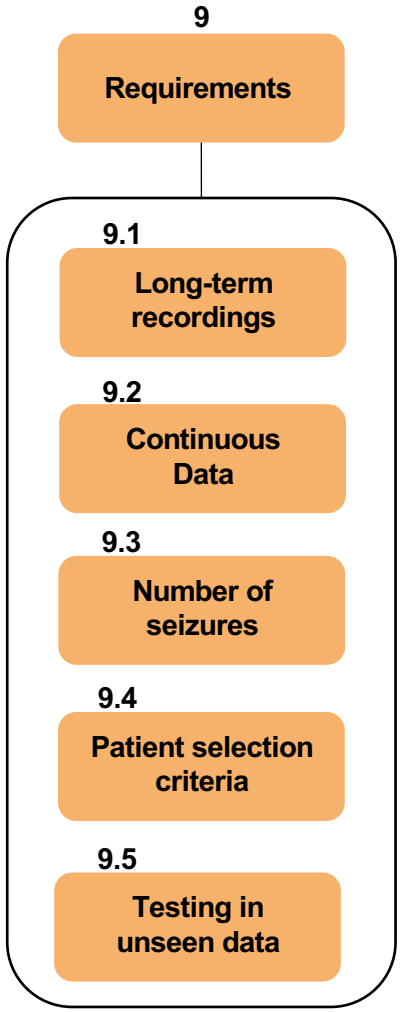


# Encapsulation of Requirements

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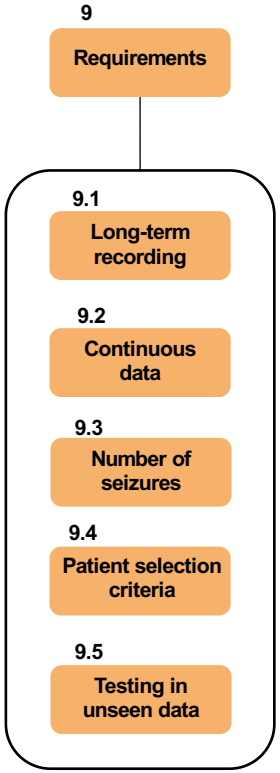
# Requirements

Studies have requirements (9), which constitute established assumptions among peers on data representativity of either real-life or a trustful proof-of-concept. By fulfilling these requirements, authors assume the best possible simulation of a real context. The testing data requirements are: long term recordings (9.1), continuous data, without manually removing any segments due to noise or artifacts (9.2), minimum number of seizures to allow for training and testing of the models (9.3), rigorous patient selection criteria (9.4) where no patient was discarded based on performance, and models tested in unseen data (9.5).

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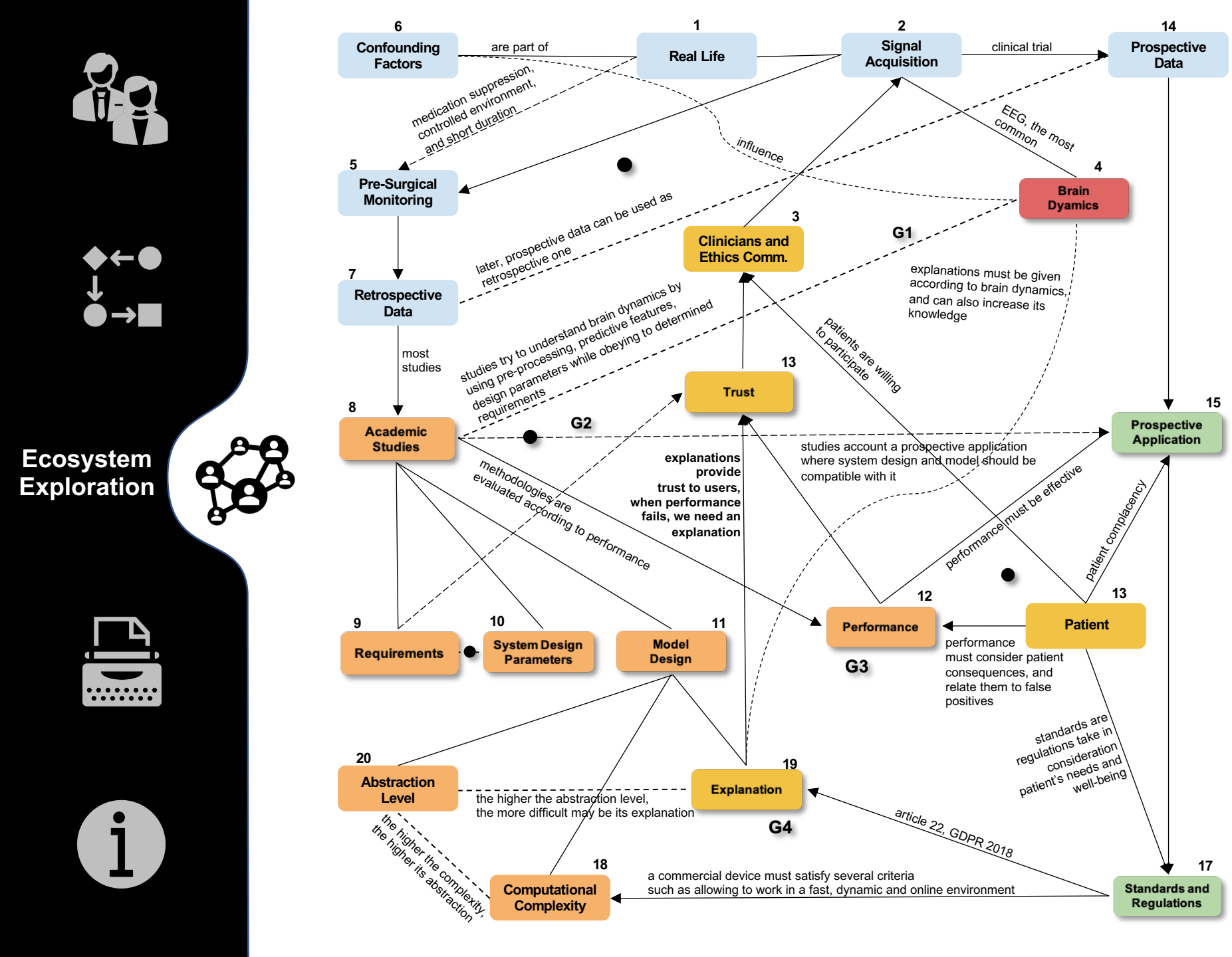
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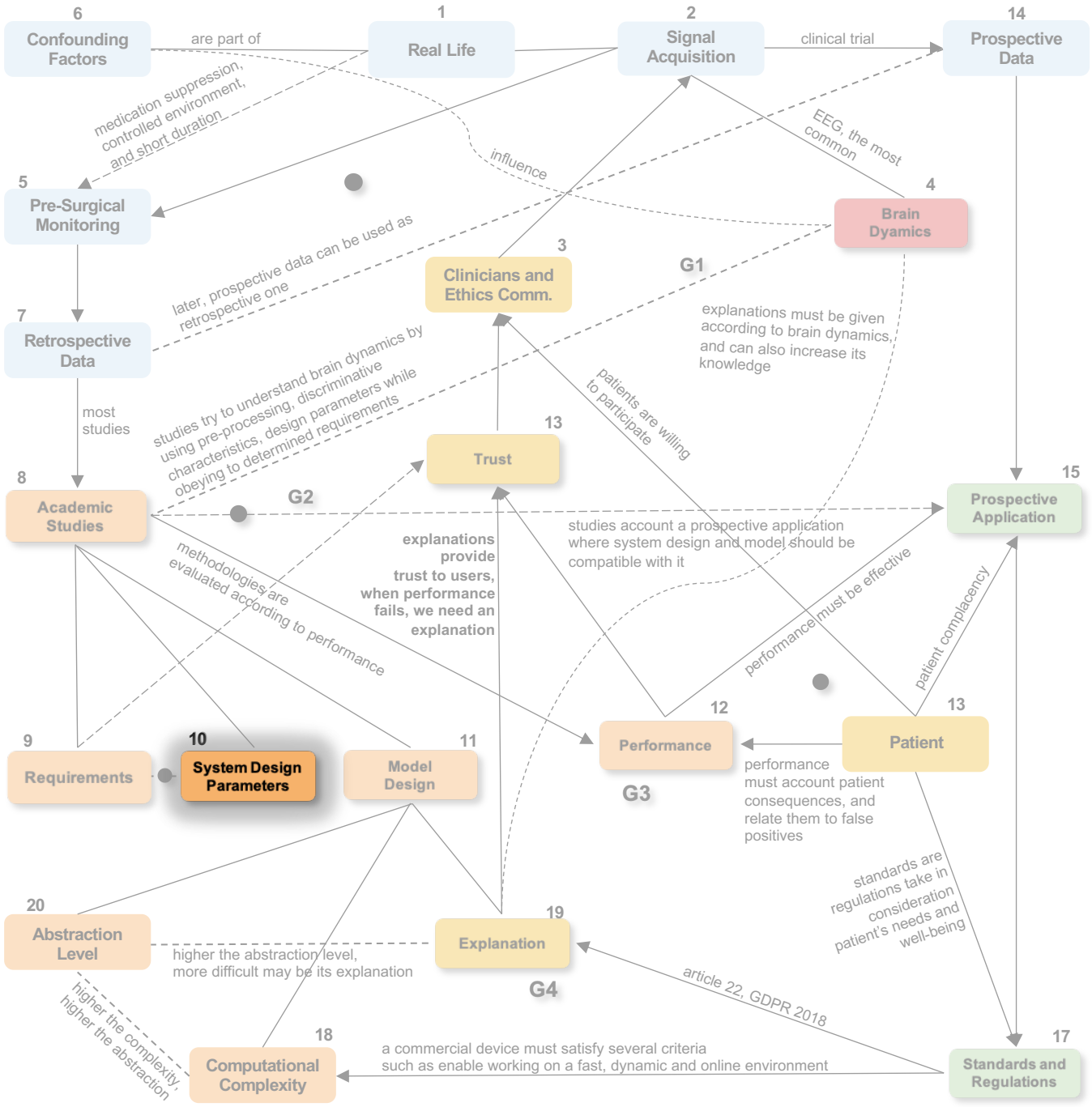
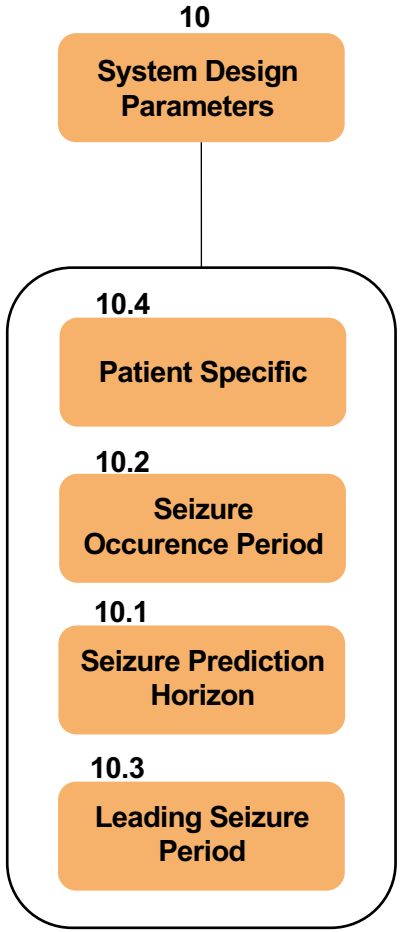


# Encapsulation of System Design Parameters

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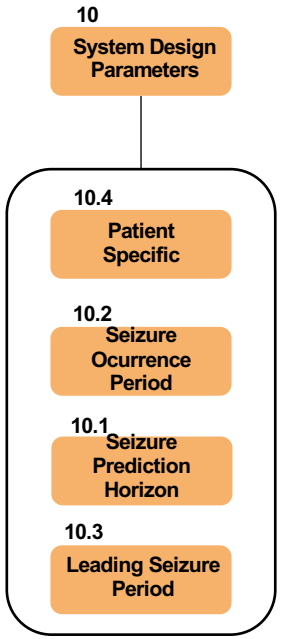
# System Design Parameters

When considering a seizure intervention, system design parameters (10) have a significant role. An alarm must be interpreted considering a Seizure Occurrence Period (SOP, 10.1), where a seizure is expected to occur, and a Seizure Prediction Horizon (SPH, 10.2), that guarantees time for an intervention. Furthermore, methodologies have converged for patient-specific algorithms (10.3) as authors have proven the existence of individual epileptic biomarkers. This influences study requirements (9- -10): patient-specific strategies require a minimum recording duration (10.3→9.1) and a minimum number of seizures per patient (10.3→9.3).

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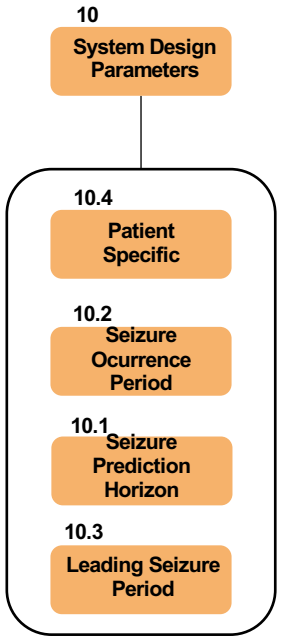
# System Design Parameters

Authors also must state the used seizure independence concept or in other words, the minimum period necessary for seizure independence (10.4). Due to brain excitability, consecutive seizures may occur in a short period. These create a cluster where the first seizure is the leading (and independent) one. It influences the number of independent seizures per patient (10.4→9.3) and also limits the amount of data that can be used. Note that there is no definition/rule to consider a seizure as independent, which represents another difficulty regarding brain dynamics (4). Additionally, it is worth noting that, authors in prediction studies with pre-surgical monitoring data, tend to use shorter periods of time for defining seizure independence comparing to a real life scenario.

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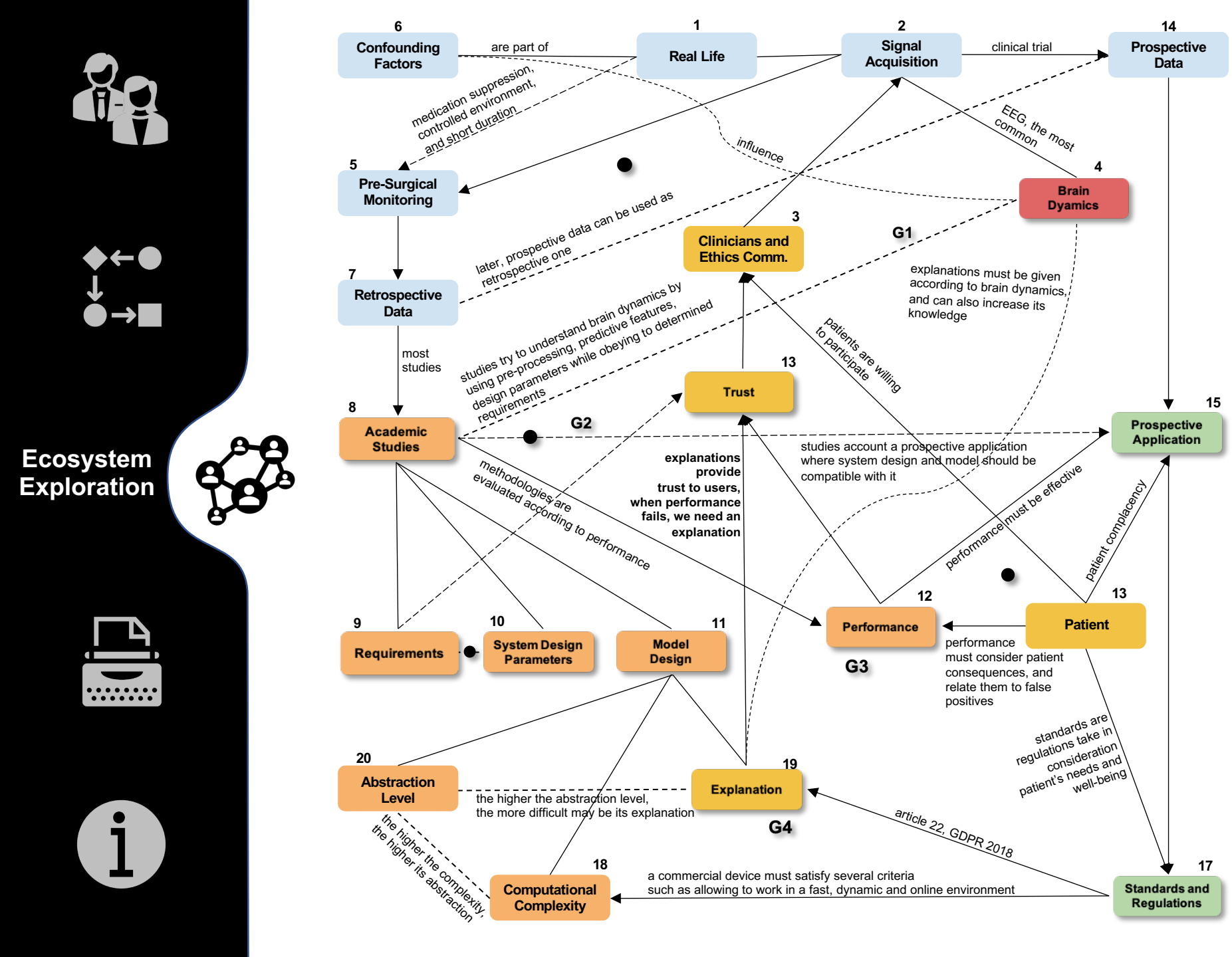
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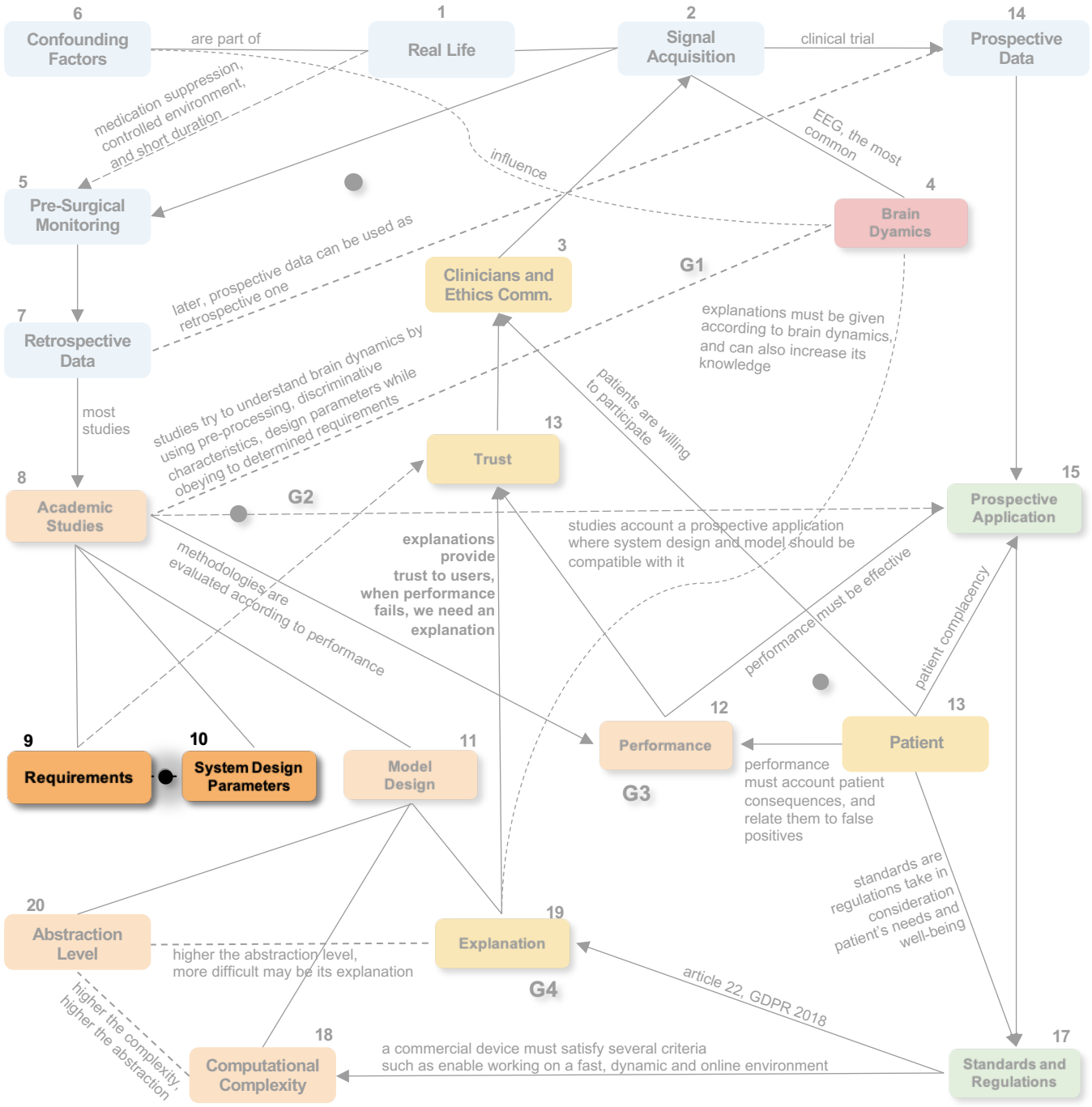
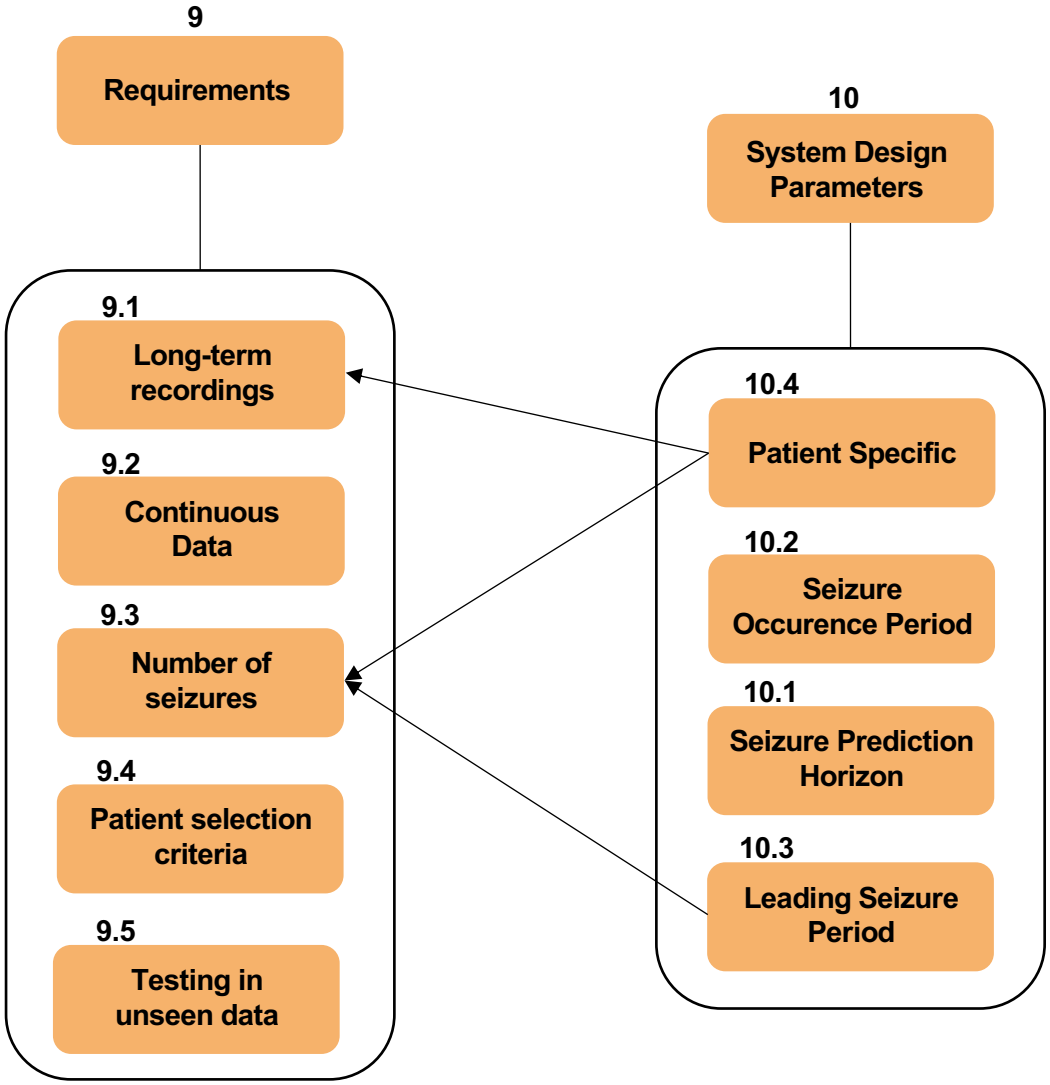


# Relation between Requirements and System Design Parameters

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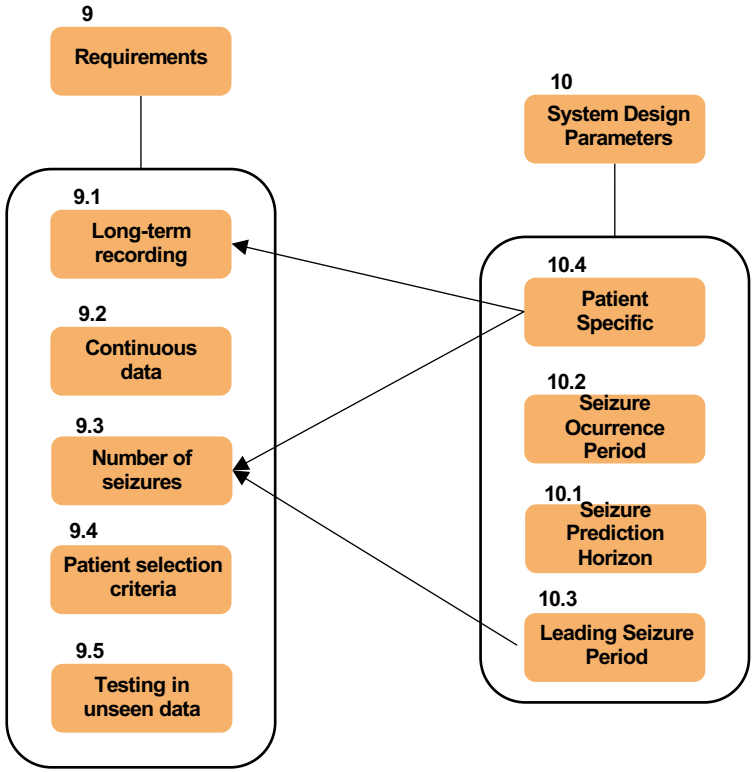
# Relation between Requirements and System Design Parameters

System design parameters influence study requirements. Patient-specific strategies require a minimum recording duration and a minimum number of seizures per patient and not for the overall set (10.4→9.3, 10.4→9.3). The leading seizure separation also influences the seizure number per patient (10.3→9.3).

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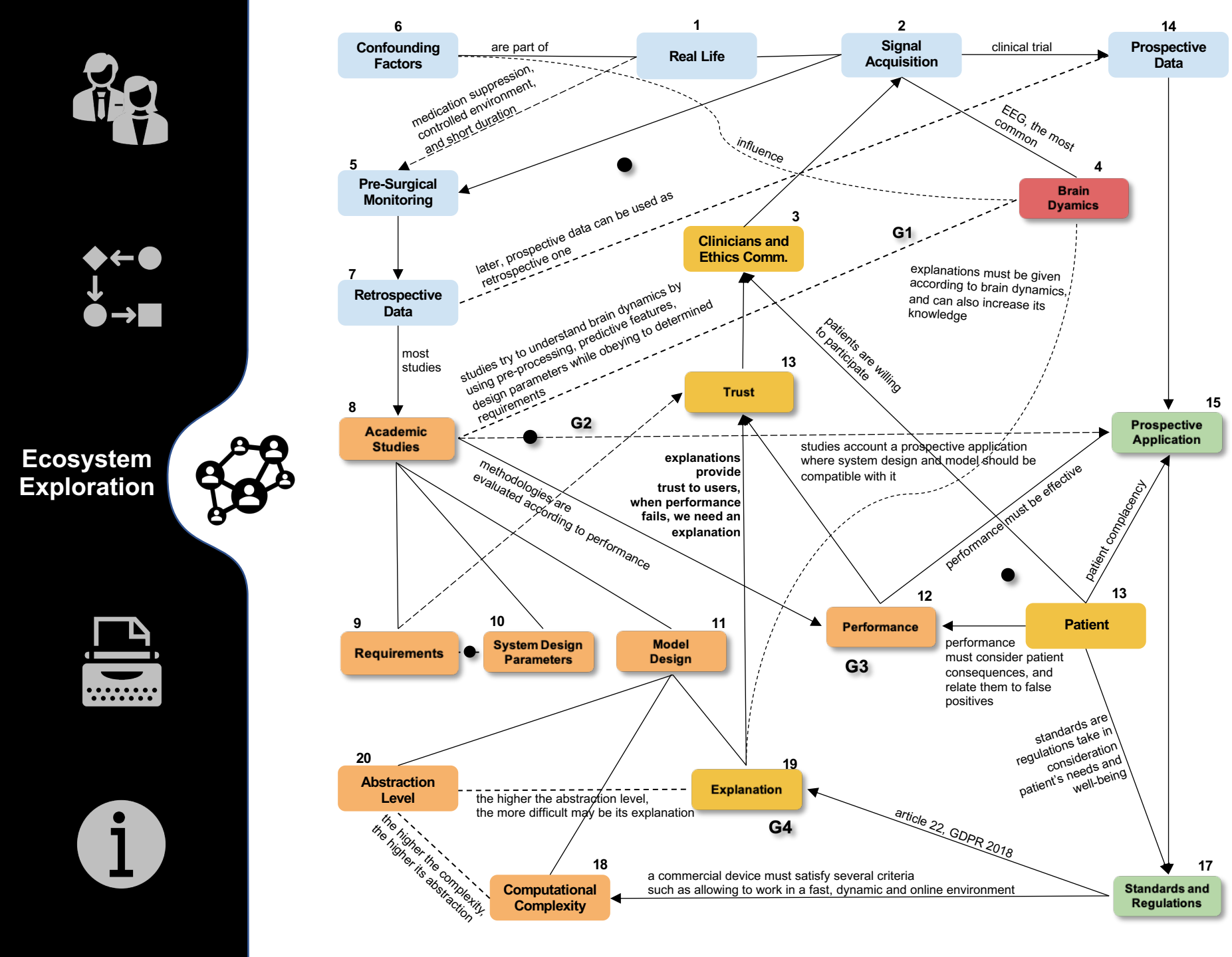
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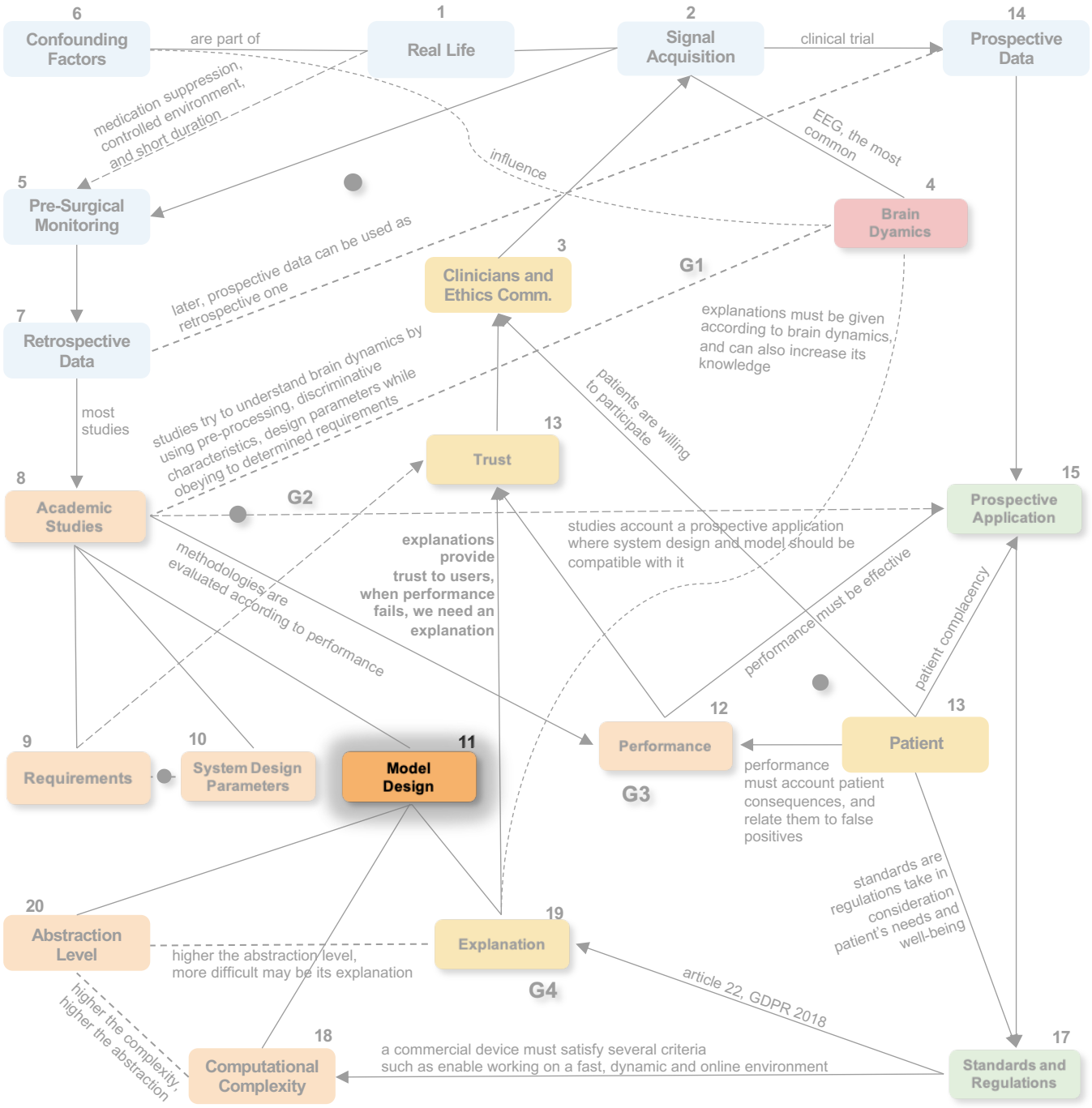
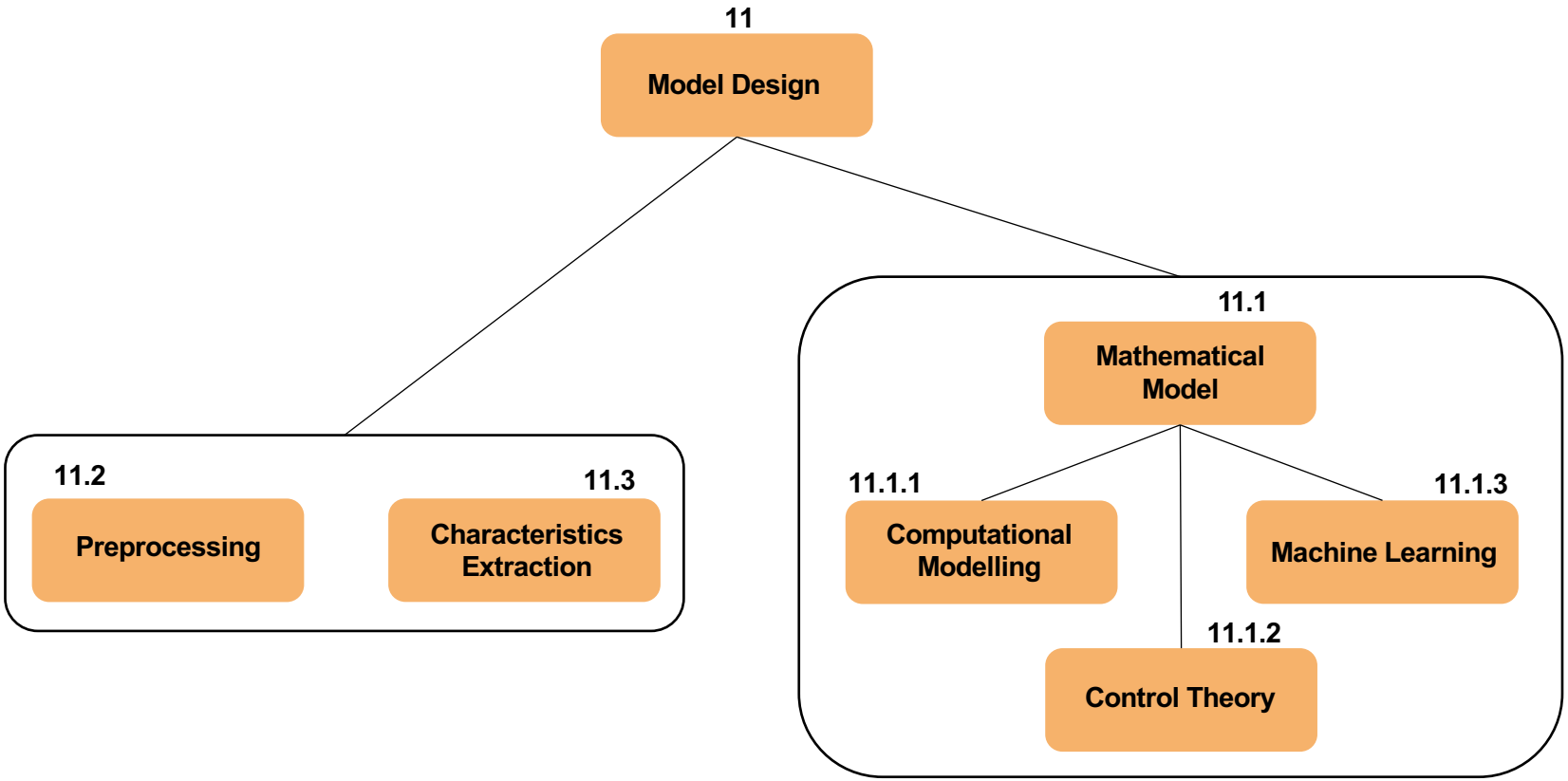


# Encapsulation of Model Design

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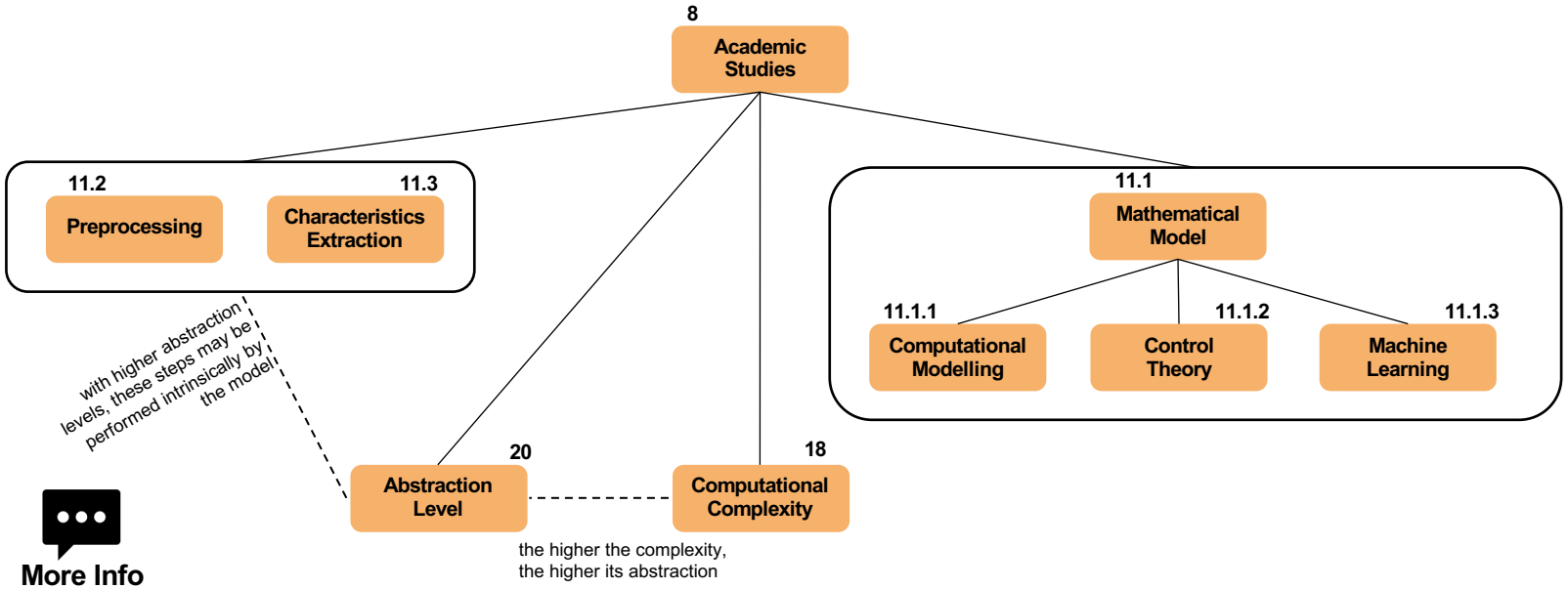
# Model Design

Seizure prediction entails the analysis of time-series, which is typically initiated by segmenting into sliding windows. Thus, a model (11) might be able to distinguish brain states (inter-ictal or pre-ictal) throughout time. This model is a mathematical approach (11.1) which uses strategies from different domains, such as computational modelling (11.1.1), control theory (11.1.2), and the most common, machine learning (11.1.3), among others.

Before training a model, authors may pre-process (11.2) the signals to remove noise while maintaining the frequencies of interest and then, they extract predictive features (11.3). These two steps may be optional as more complex mathematical models have the theoretical potential to handle raw signals. A model, especially a machine learning one, can be distinguished by its abstraction level (20). Briefly, higher abstraction methods may intrinsically perform signal pre-processing (20- -11.2) and feature extraction (20- -11.3). Another relevant factor is computational complexity (18), where higher abstraction levels usually require higher processing power for algorithm developing (18- -20). This can be an arising problem for real applications (17→18) as low computational requirements may be necessary.

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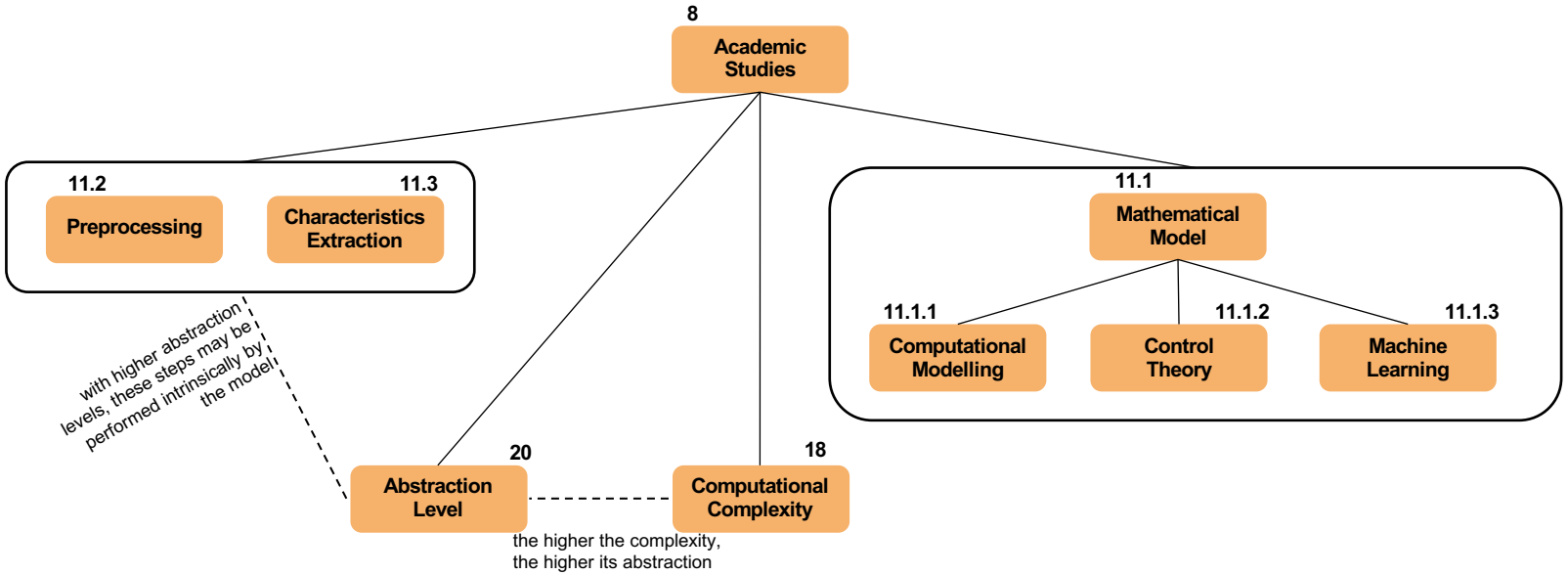
# Model Design

Despite not mentioned directly, by choosing a given preprocessing method, feature, and model, we may be undertaking several assumptions on a physiological signal. Therefore, when constructing a pipeline, we challenge authors to inspect them. Here is a list of questions one can ask: is the signal stationary, does it have noise, is it the result of linear interactions? Are the assumed brain dynamics simple or complex? Do they involve interactions? Although these may not change the experimental design, they can improve discussion and consequent comparison (see Supplementary Material: "Assumptions" section).

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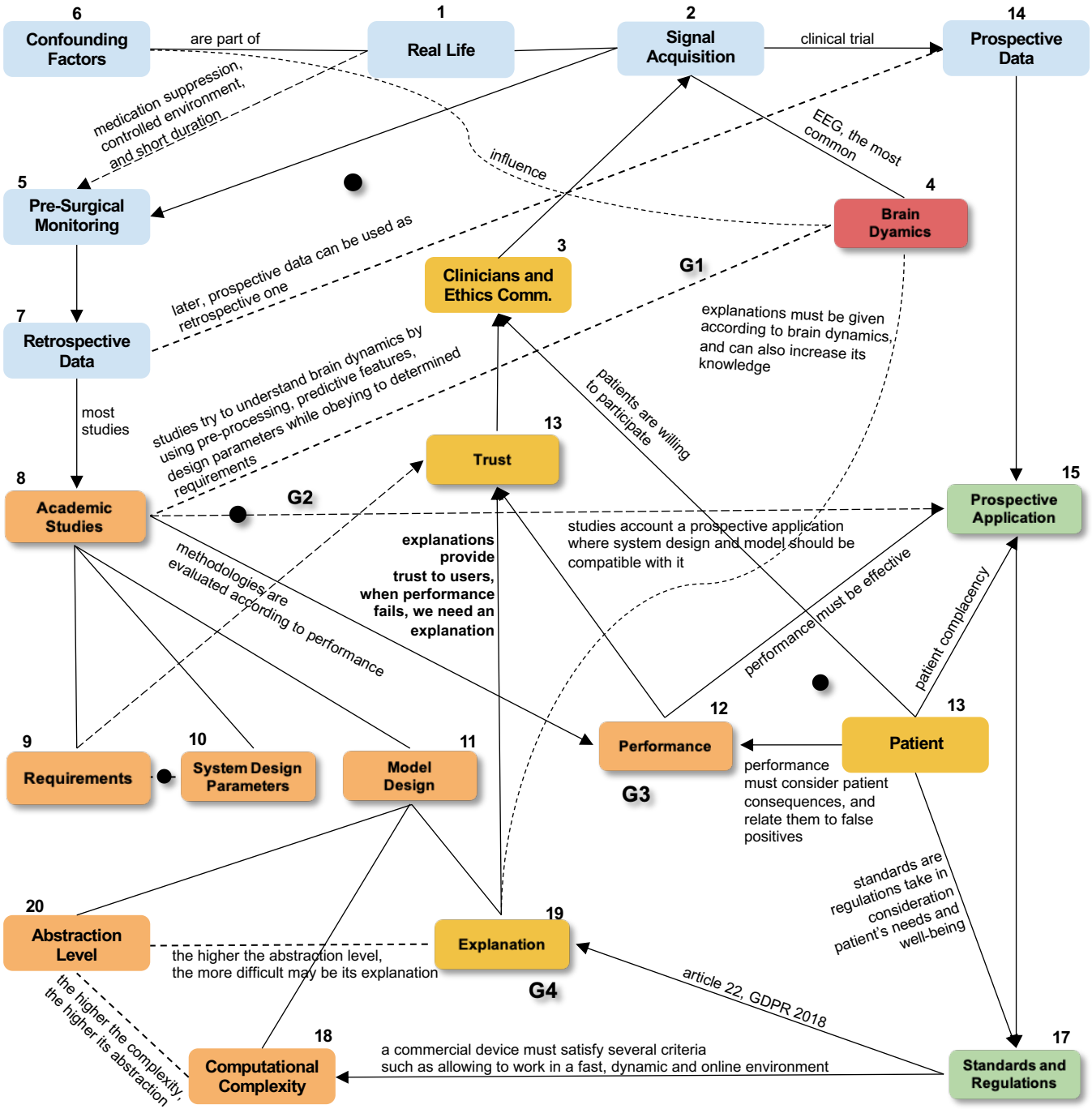

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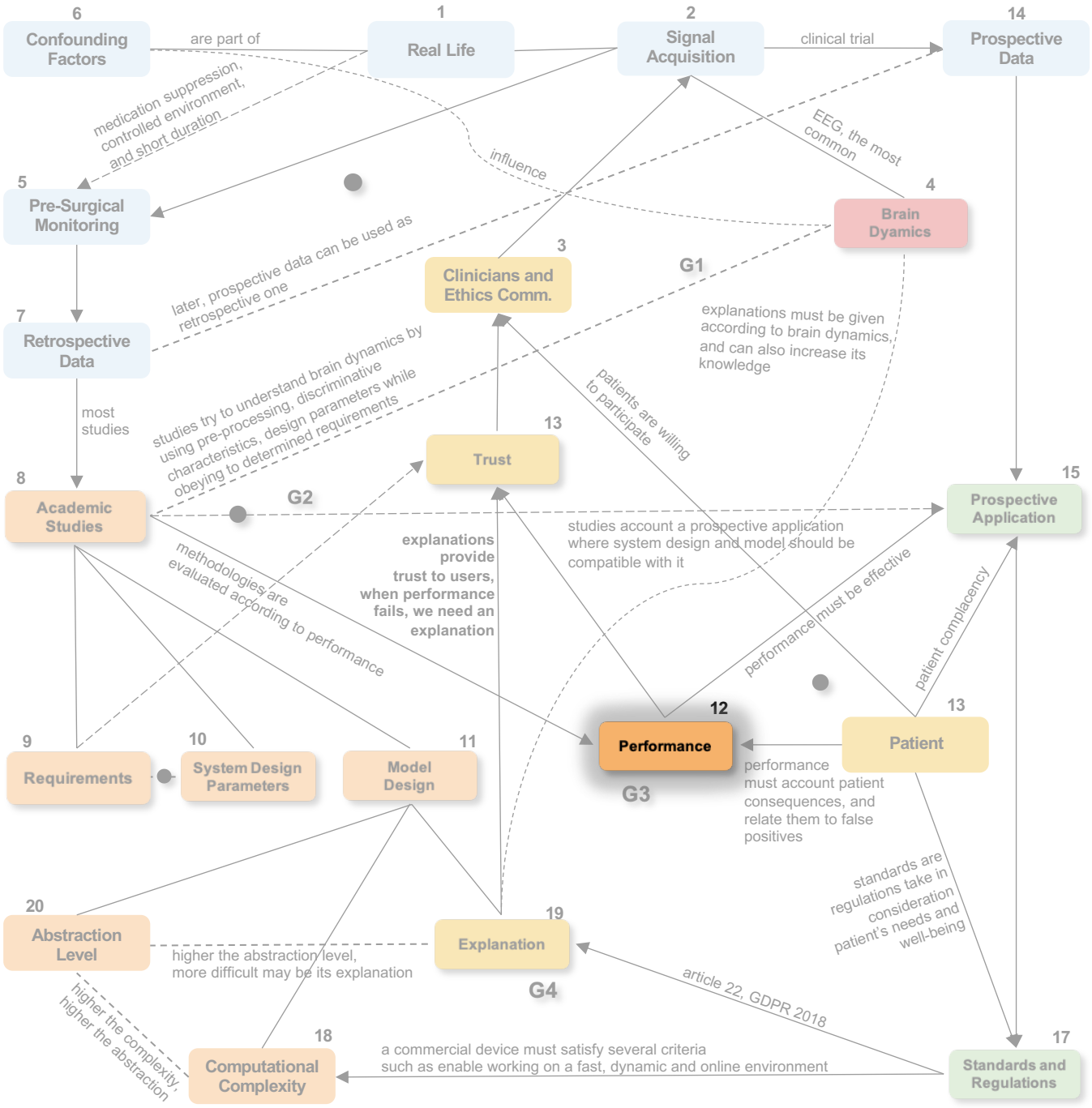
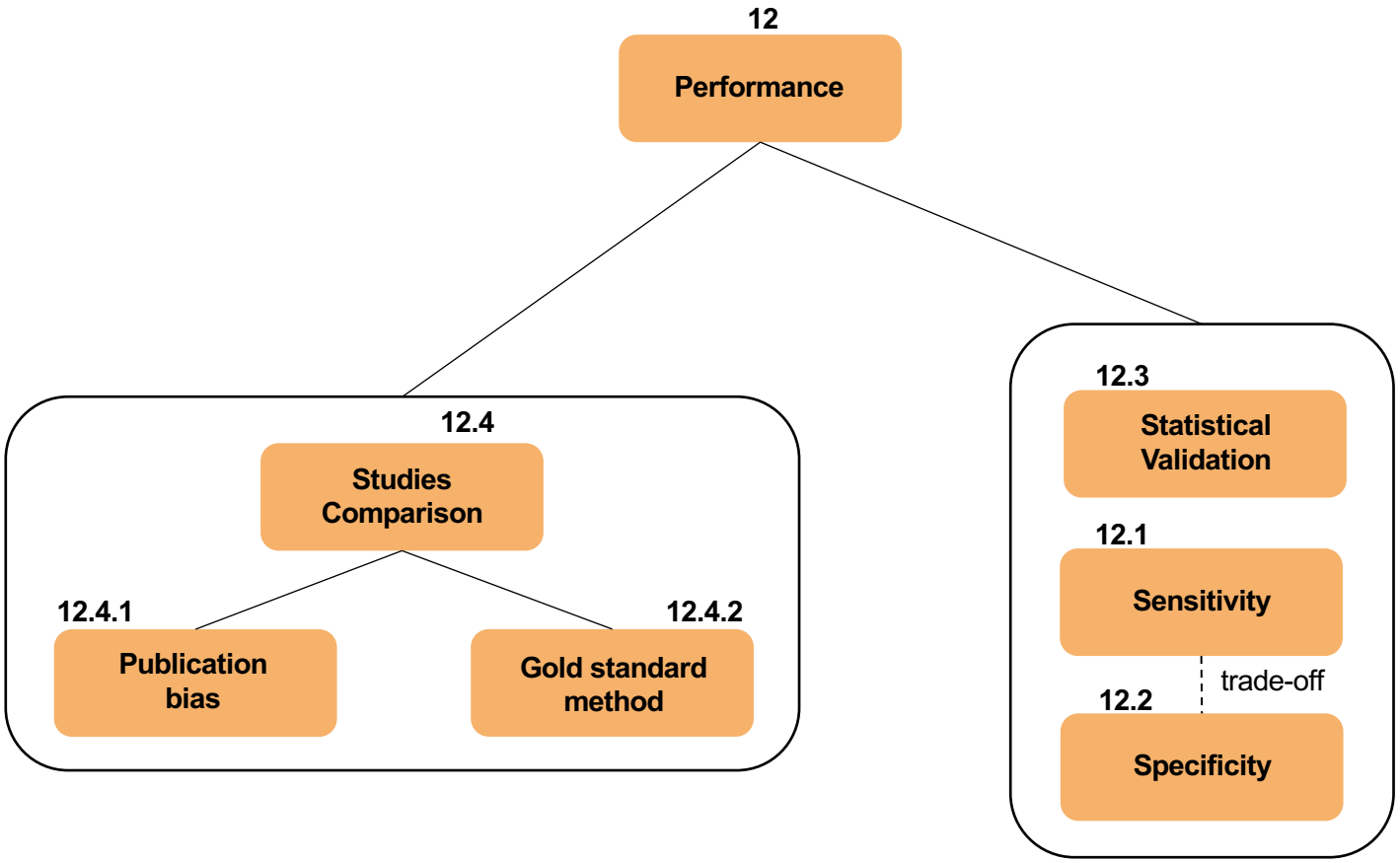


# Encapsulation of Performance

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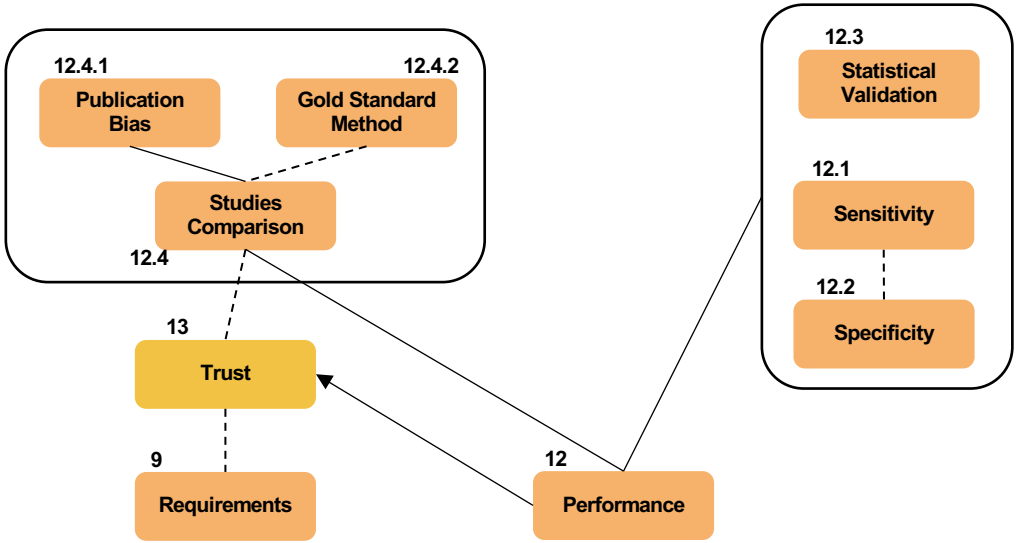
# Performance

Performance is one of the most discussed aspects in seizure prediction studies. A promising methodology is naturally associated with model performance, which increase trust in the correspondent study (12→13). Sensitivity (12.1) corresponds to the ratio of correctly predicted seizures. Specificity (12.2) quantifies the number of false positives and is commonly obtained by counting the number of false alarms per hour (FPR/h).

Statistical validation (12.3) has the goal of understanding if performance is above chance level as there is a trade-off between sensitivity and specificity (12.1- -12.2). In other words, this validation makes it possible to understand if the model's performance is the result of the identification of random oscillations in the biosignals rather than seizure-related patterns. This aspect becomes more relevant considering that seizure predition is a rare-event problem with considerable imbalance between inter-ictal and pre-ictal intervals.

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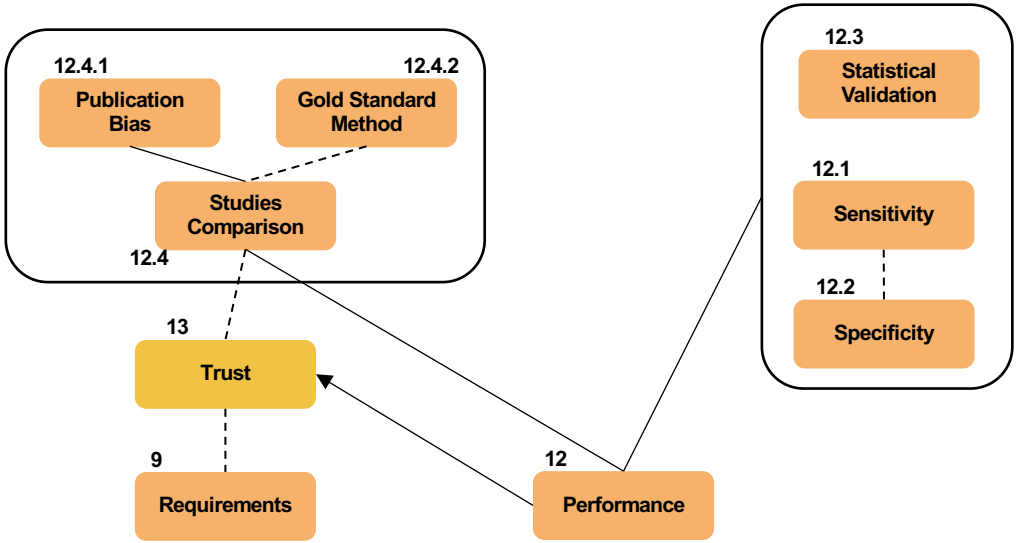
# Performance

Studies comparison (12.4) enables to find methodologies that perform acceptably in different datasets and contexts, while handling publication bias (12.4.1). This may occur when using retrospective data while trying several methodologies. When authors only report the best results and do not interpret failures as advances, their studies show overestimated performances or, in other words, overfitting to the tested data.

Proper comparison of studies requires more than comparing similar metrics. Authors are strongly recommended to use statistical validation to prove that the developed models overcome a random predictor in terms of performance. Nevertheless, it would be appropriate to compare results with a gold standard methodology applied in the same conditions.

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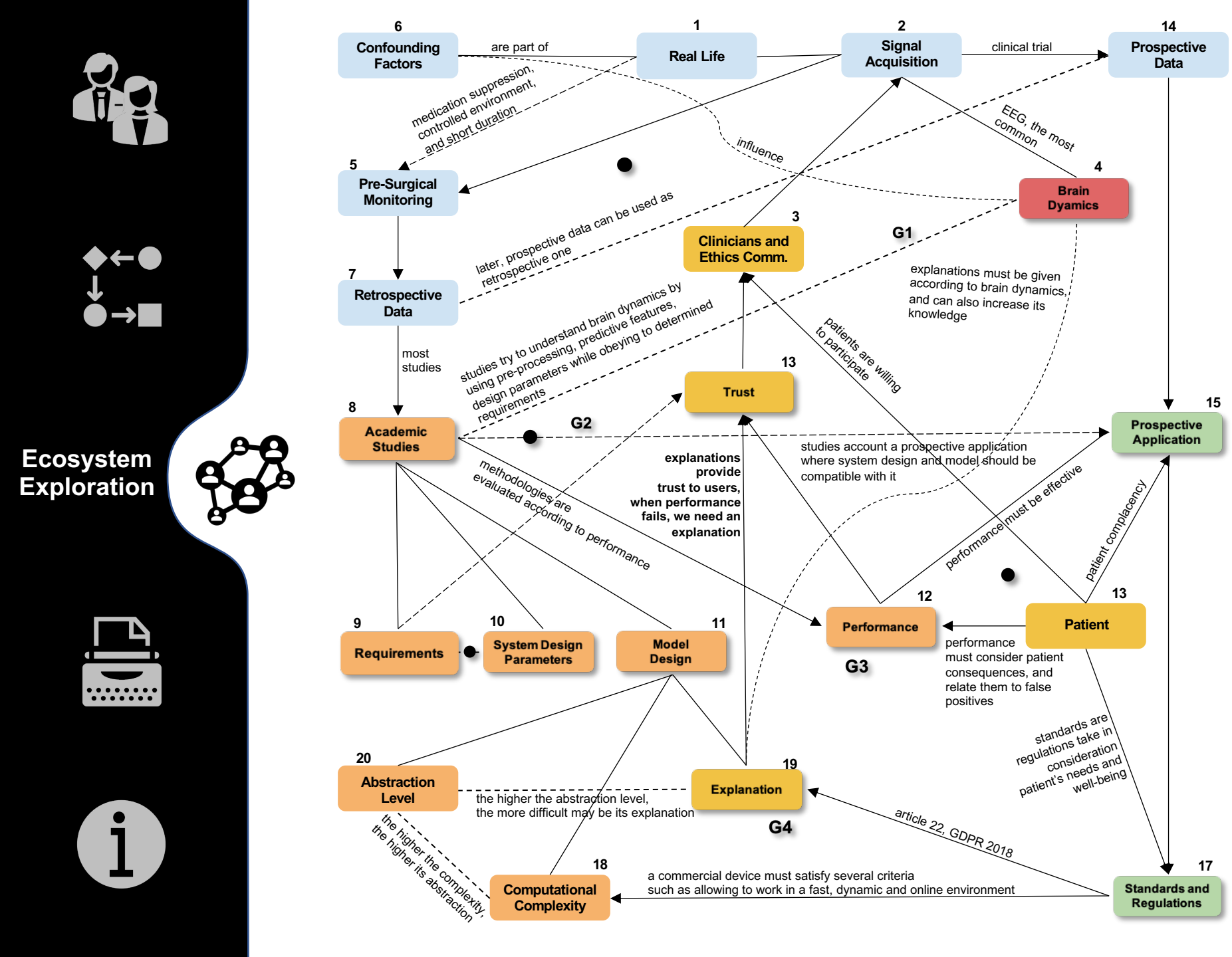
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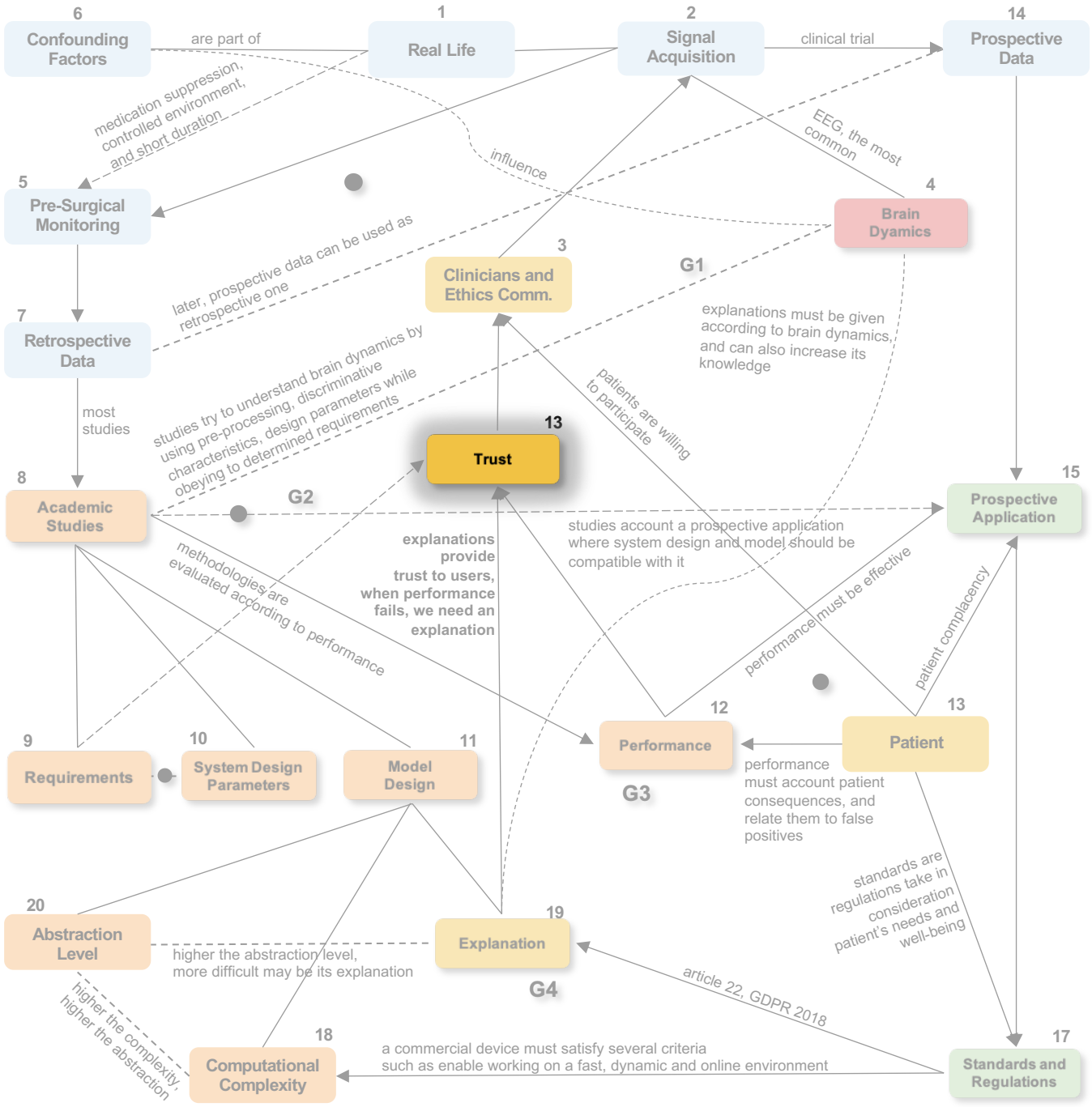
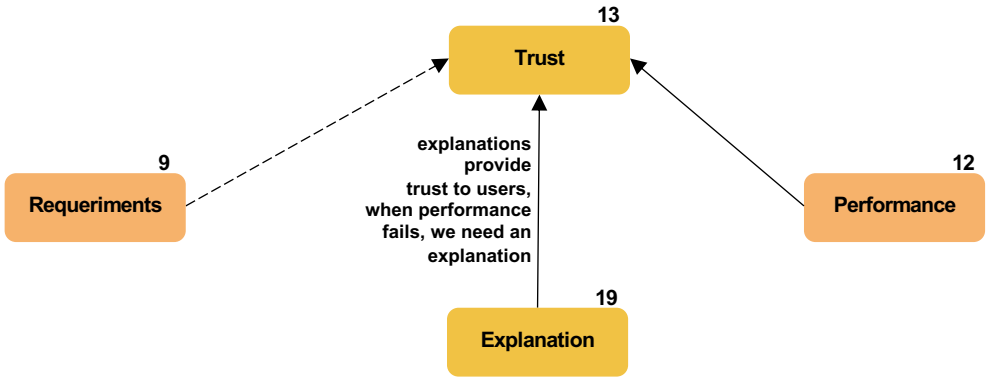


# Trust

After proper studies comparison, one can ask what is a good performance or even inquire about the minimum performance that justifies the design of a clinical trial. We believe that a proper methodology is one which we trust. In literature, trust seems to be represented by studies reporting high performance (12→13) and complying with consensual study requirements (9- -13). By analysing data from longer recordings and/or higher number of patient, trust increases as the testing data is more likely to represent real-life conditions.

Although a given methodology, eventually, makes incorrect decisions, we can still trust it if one can explain its decisions (19→13). A great scepticism concerning machine learning and high-level abstraction models may be due to the difficulty in delivering explanations about models' decisions. Although authors and/or clinicians are more willing to trust black-box models when they make correct decisions, wrong ones lead to mistrust because there is no human-comprehensible explanation.

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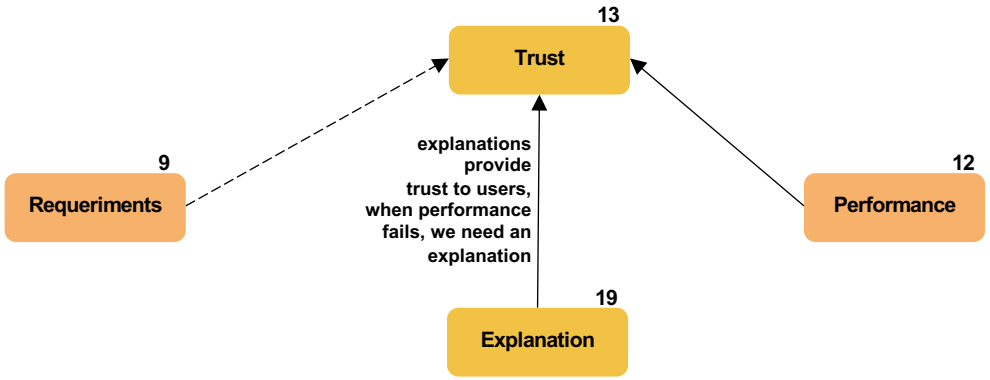
# Trust

The phase IV Neuropace RNS® system (NCT00572195) can use up to two independent detections, which are highly configurable and adjusted by the physician, which ensures patient safety. Each detection performs a threshold decision, based on a given extracted feature (line-length, bandpass, and area), by comparing the current window of a analysis with another considered to have inter-ictal activity. We believe this is the most simple and explainable strategy we can obtain. One can fully understand the underlying mechanisms behind each decision.

The phase I NeuroVista Seizure Advisory System (NCT01043406) is more complex, using a pre-processing step, extracting similar and intuitive features (line-length, Teager-Kaiser energy, and average energy), and training a machine learning model that produced a measure of seizure-risk which concerns a seizure-susceptibility state. This model uses as input the best 16 features (from a set of 16 channels X 6 filter/normalization options X 3 analysis methods), and it involved 10 layers (creating different decision surfaces), being inspired in k-nearest neighbours (k-NN) and decision tree classifiers, where each layer considers a different seizure-risk related to its proximity to a seizure event.

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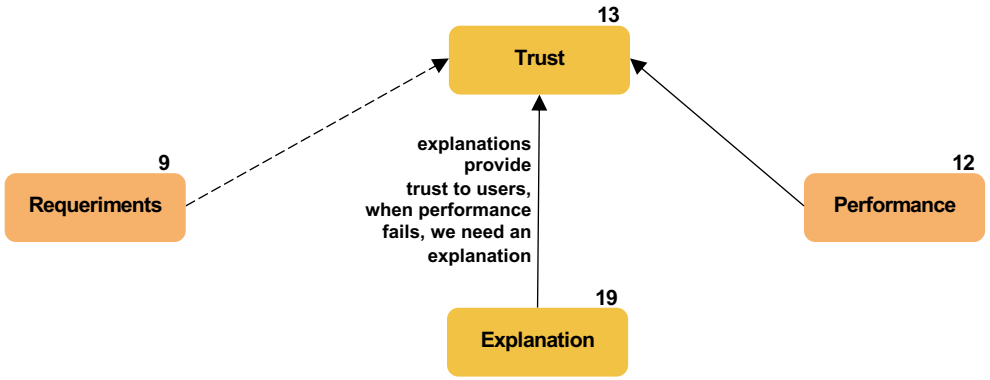
# Trust

Neurovista Advisory System algorithm is more complex and not fully transparent. In other words, we do not understand its underlying mechanisms, despite espiried and k-NN and decision tree classifiers (which may be intrinsically interpretable when using a reduced set of features). Calculating seizure risk in a 16-dimension feature space that is furthered divided into $2^{10}$ partitions (decision surfaces) it is not human comprehensible.

Nevertheless, the extracted features are clinically intuitive and the model decision can produce a very human-intuitive output explanation on the obtained seizure risk. It simultaneously compares the current window of analysis with several data distributions whose time proximity to a seizure (and therefore, seizure risk) is considered. By performing a multiple data-distribution classification, it may be more robust to data bias and noise. The authors also ensured patient safety: firstly, they accessed model performance on pre-acquired patient-specific data and secondly, only patients with satisfactory performance received the advisory system.

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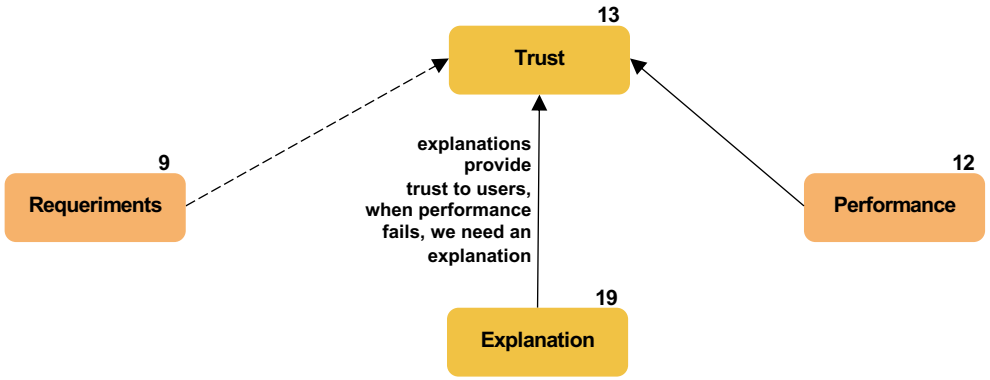
# Trust

These two clinical trials demonstrate that, despite all the scientifc community efforts to develop complex models and consequent increase in performance, it may be necessary a fully explainable model to provide trust. Additionally, the Seizure Advisory System clinical trial demonstrates the possibility of using models that are not necessarily intrinsically interpretable, as long as they produce human-comprehensible explanations, while ensuring patient safety, handling data bias, and achieving model robustness.

Trust should be a matter of concern when one designs a study. High-level abstraction models may have the potential to handle complex dynamics but require strong efforts towards providing explanations (19- -20). Current clinical knowledge on physiology should be the source of explanations as well as the basis for new findings (19- -4). As an explanation is an exchange of beliefs, its acceptance may differ among patients, clinicians, and data scientists.

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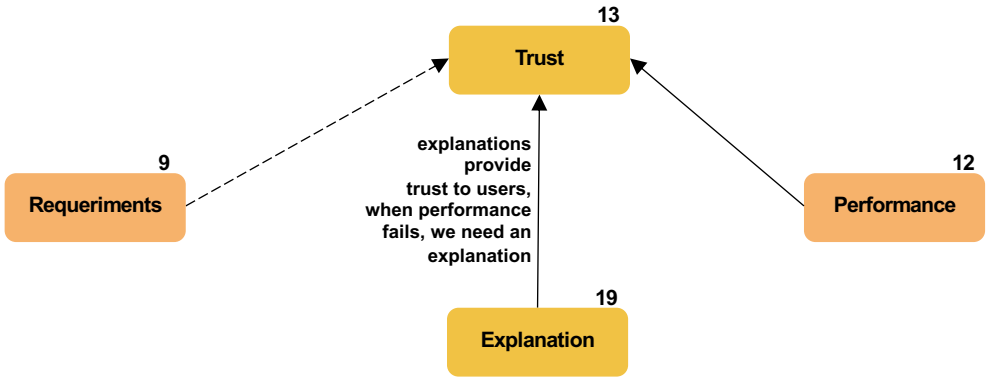
# Trust

Note that we did not consider a possible relation between patient and trust (16→13) as it concerns solely the algorithm design. Additionally, we also did not mention any connection between patient and explanation (16→19) directly, despite considering that a patient has the right for an adequate explanation concerning the device decisions. In fact, such rights are covered on article 22 from 2018 General Data Protection Regulation (GDPR).

We believe that explanation and trust concern field experts, such as data scientists and clinicians. Nevertheless, patient comfort, trust and a proper explanation are fundamental. Therefore, we implicitly included these on the relation from patient to the ethics committee (16→3), represented by the act of volunteering. When a patient volunteers, he/she demonstrates trust in researchers and clinicians, having these already shown commitment to his/her well-being and ensured an adequate explanation.

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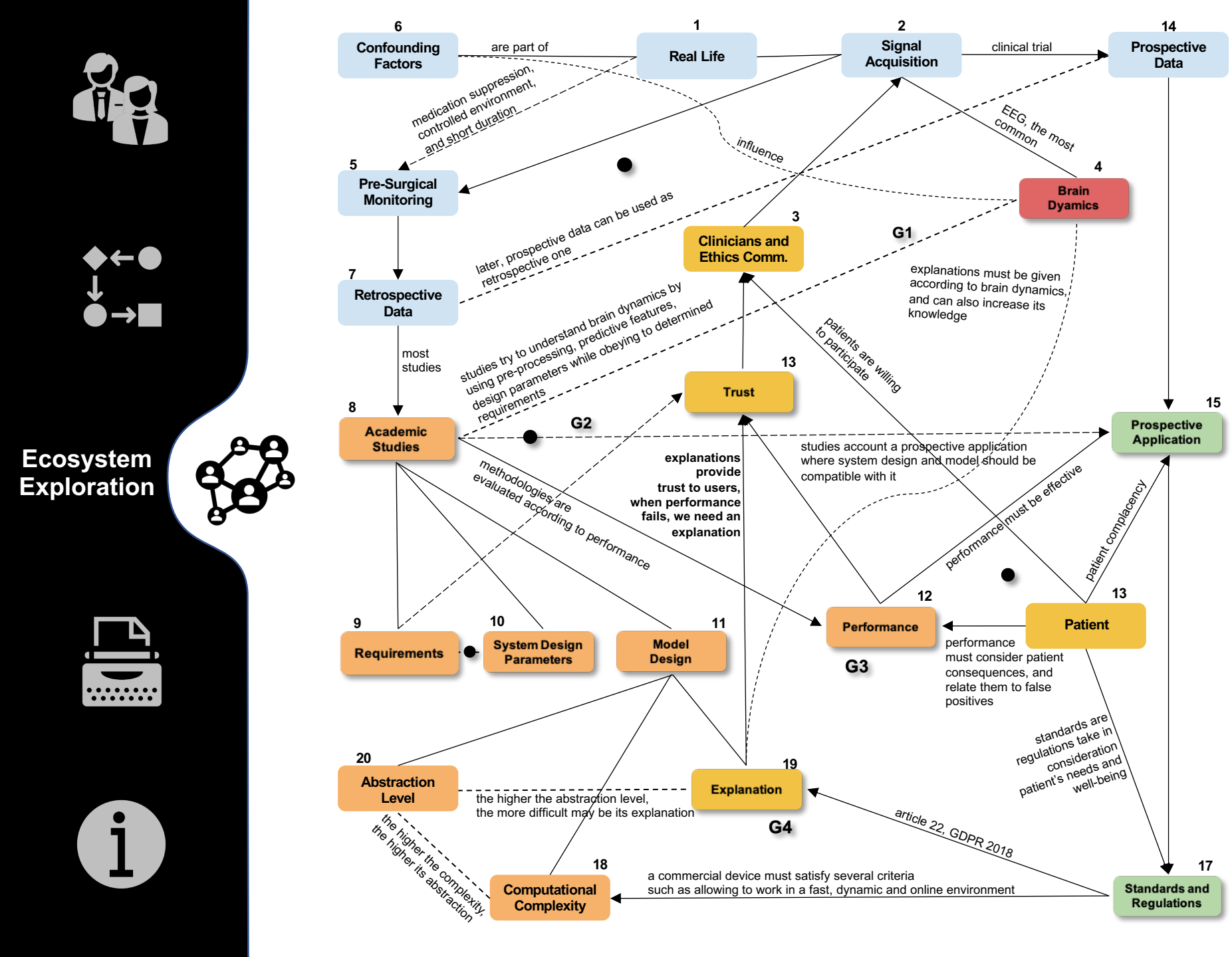
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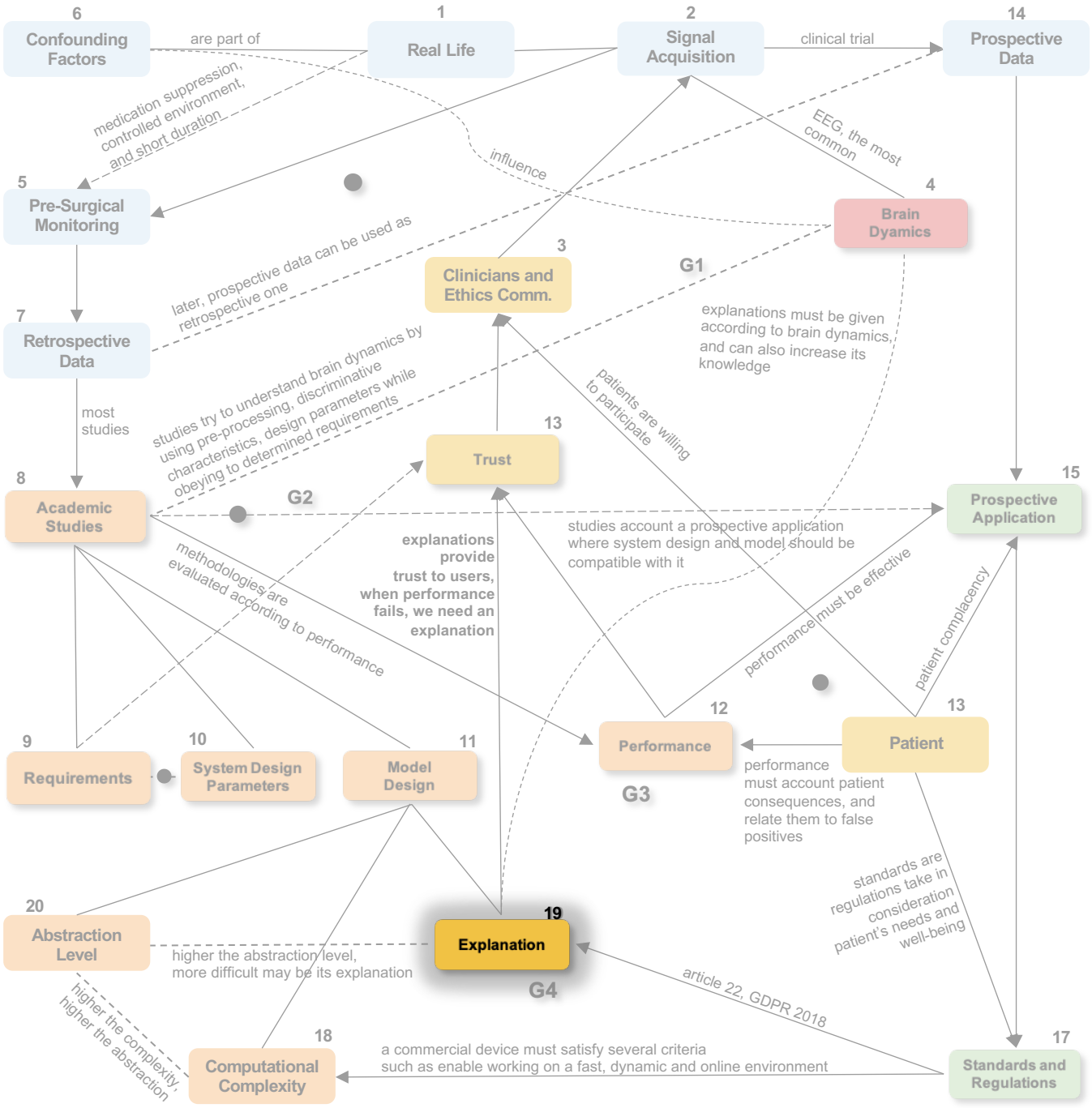
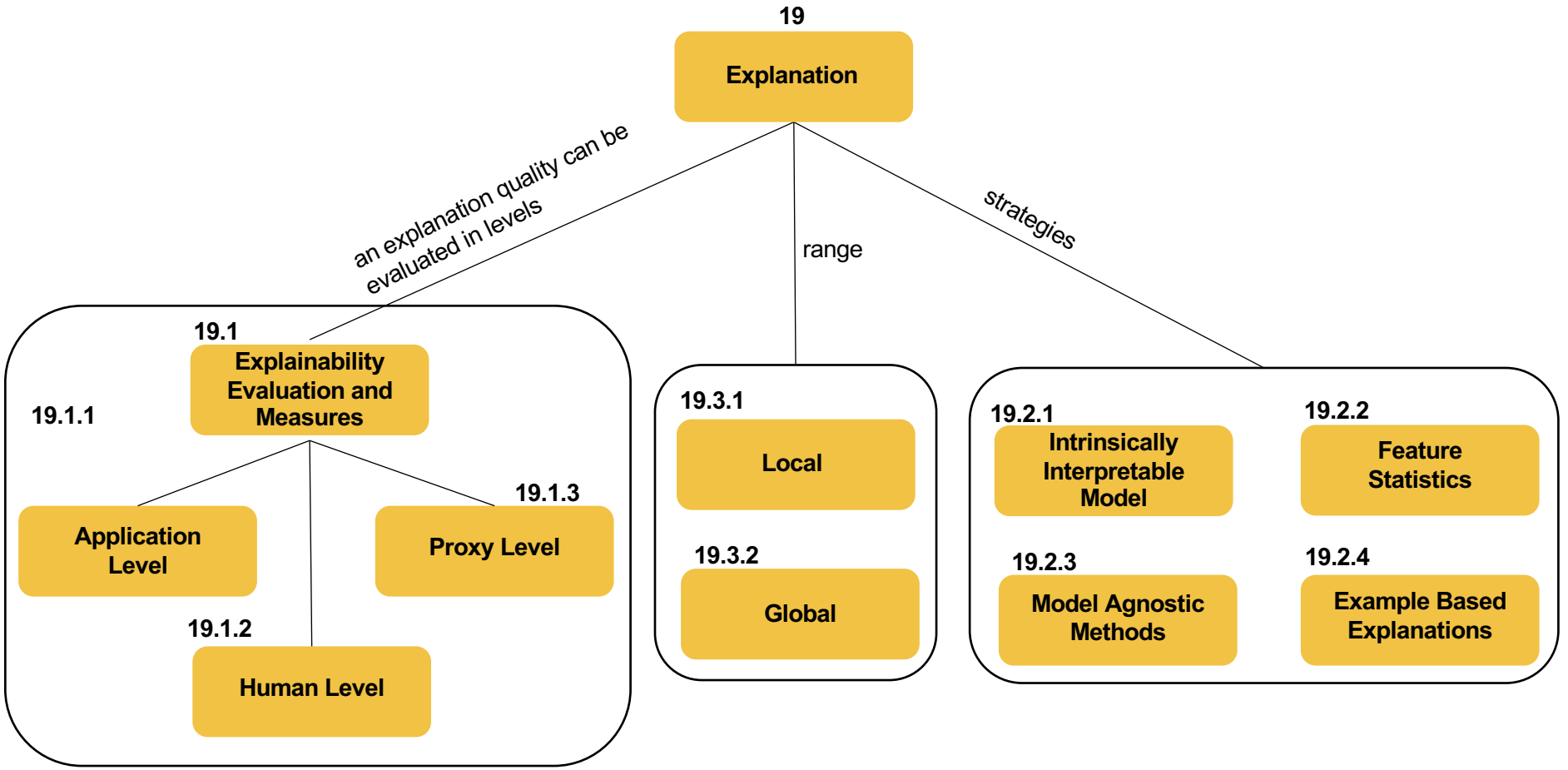


# Encapsulation of Explanation

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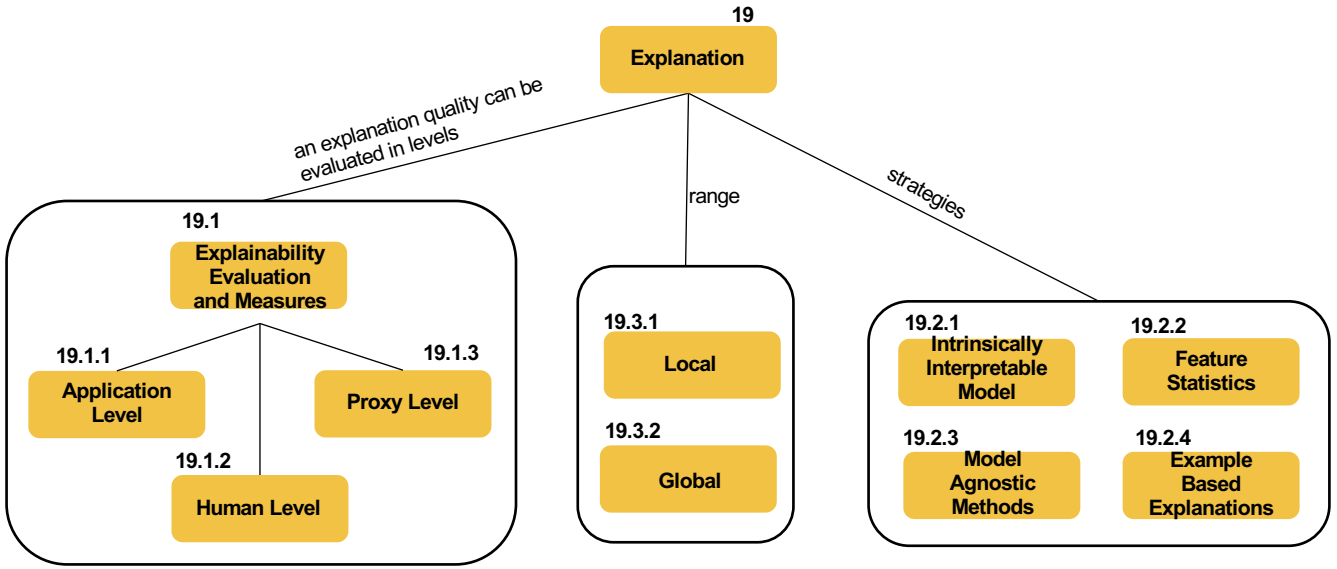
# Explanation

Explainability evaluation (19.1) is required. We can evaluate an explanation on three levels: application (19.1.1) where it must satisfy an expert (e.g. a clinician and a data scientist); human (19.1.2) where it must explain the decision to a person with no field knowledge (e.g. a patient); and proxy (19.1.3) by establishing concrete criteria (e.g. the depth of a decision tree). The proxy level is the one requiring fewer resources. Nevertheless, it should be used with great care when a model has not proved its quality in delivering explanations, both in application and human levels.

There are several strategies to retrieve an explanation which can be grouped in: i) intrinsically interpretable models (19.2.1) with a reduced set of features (such as decision trees, generalized linear models, k-NN, among others); ii) feature statistics (19.2.2) summary and visualization; iii) agnostic methods (19.2.3) which work on top of developed models; and iv) example-based (19.2.4) by representing determined samples and showing the model decision. The explanation range is also a topic of concern. It is local (19.3.1) when only explains a given decision for a sample and respective neighbourhood. If it explains all samples, it is global (19.3.2).

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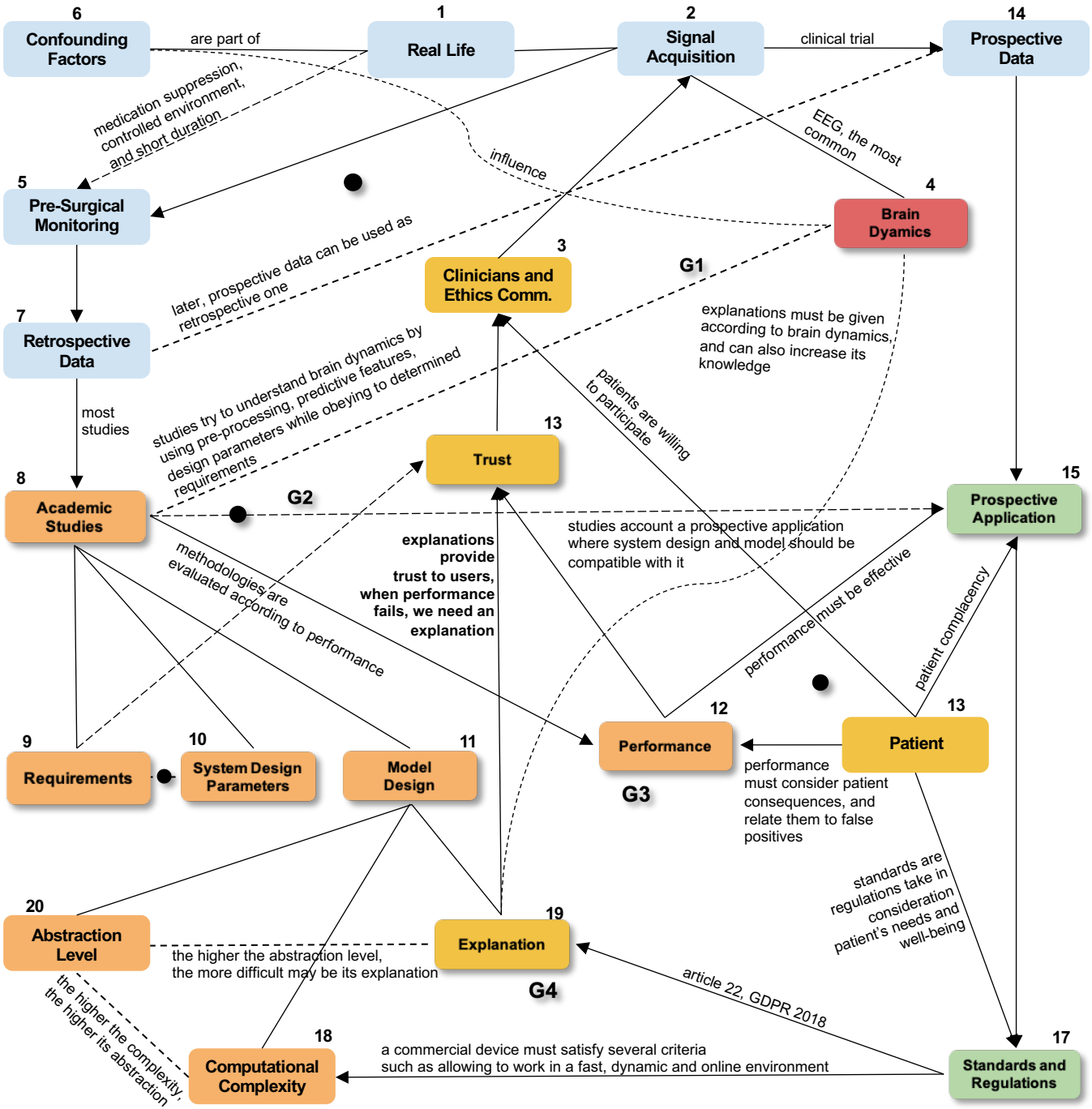
## Ecosystem Exploration



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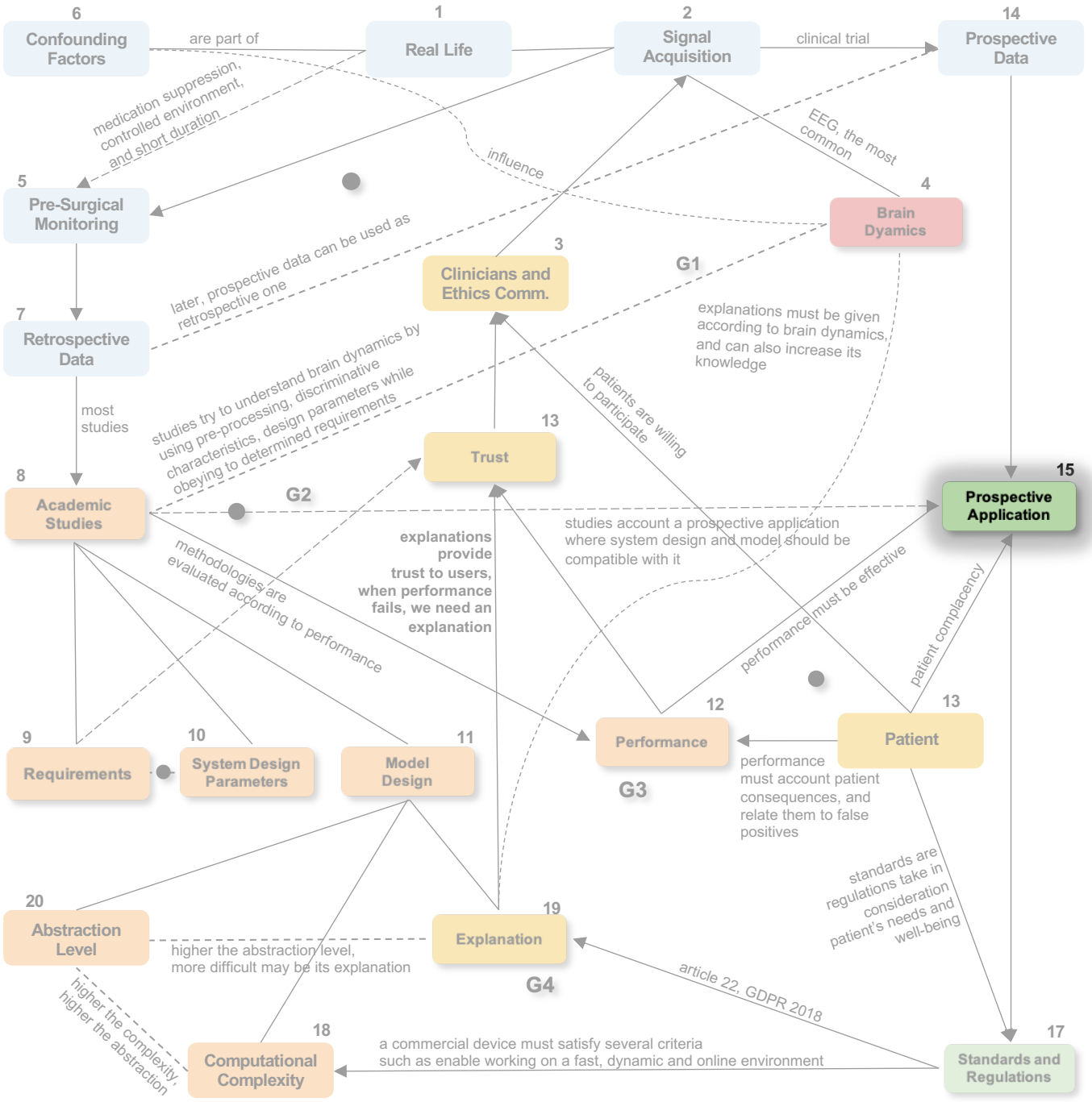
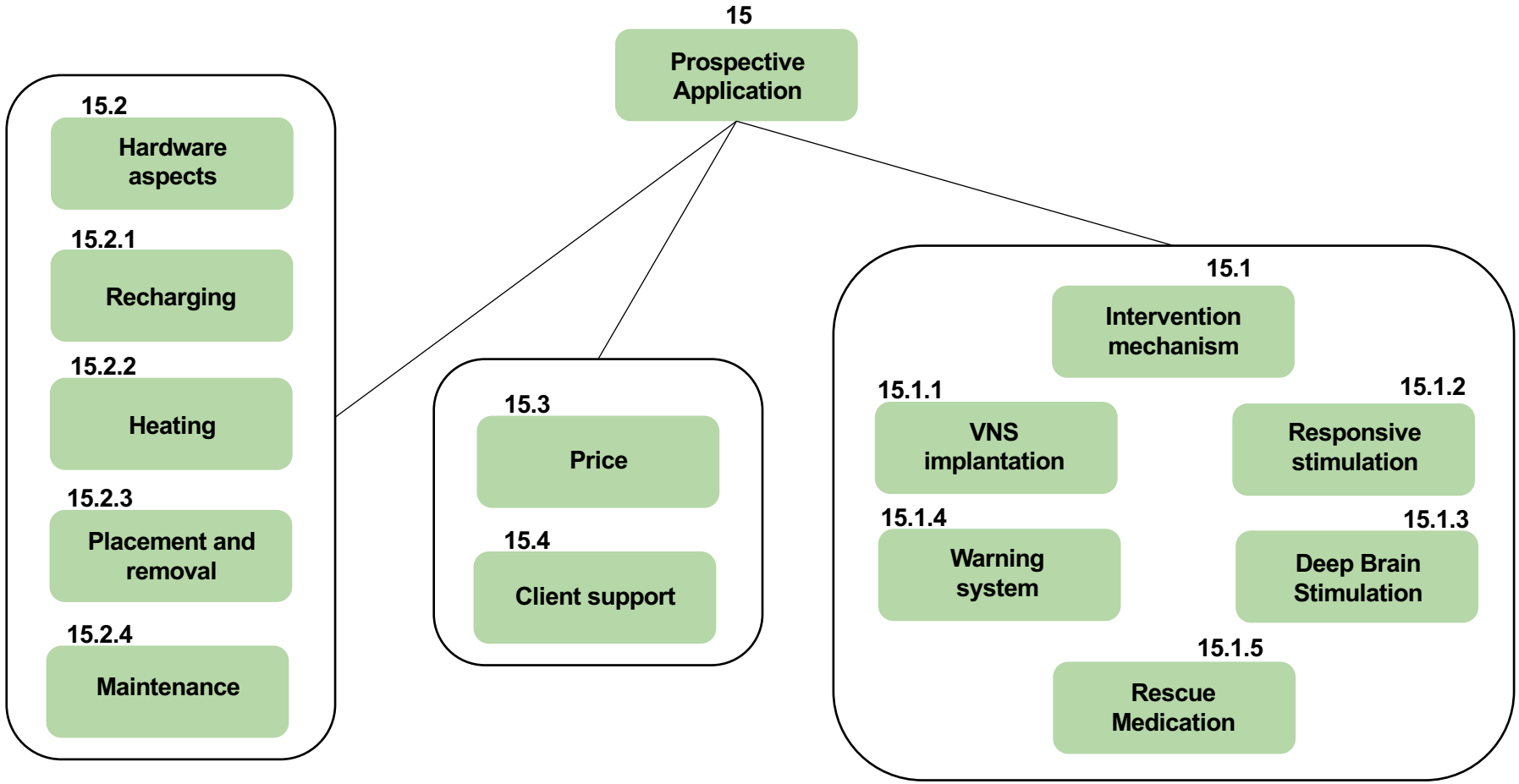


# Encapsulation of Prospective Application

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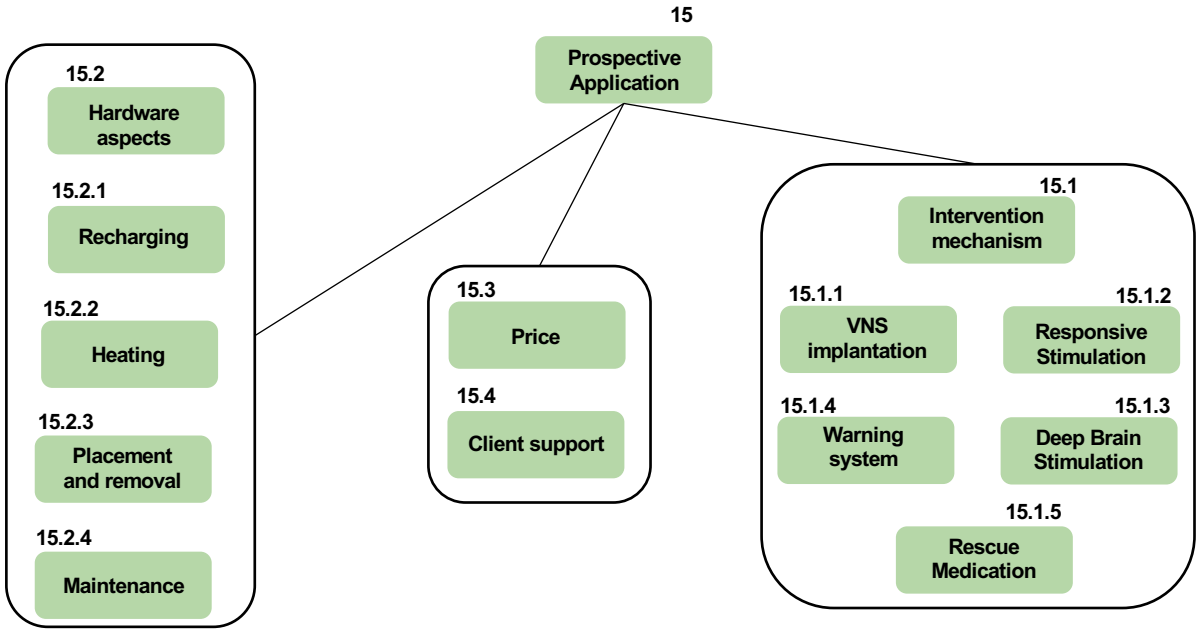
# Prospective Application

A methodology can be clinically approved (3→2 and 2→14) after years of research when it becomes trustworthy to experts, and patients are willing to volunteer. Studies are trustworthy when they report high performance and good explainability while fulfilling all data requirements.

Ideally, studies envision and open the way to the enrollment in potential prospective testing (8- -15). It is also possible to undergo a clinical trial without seizure intervention, as happens with the ongoing SeizeIT2 clinical trial (NCT04284072). These studies may not achieve the goal of disarming a seizure yet, but they present a good compromise between patient safety and research progress.

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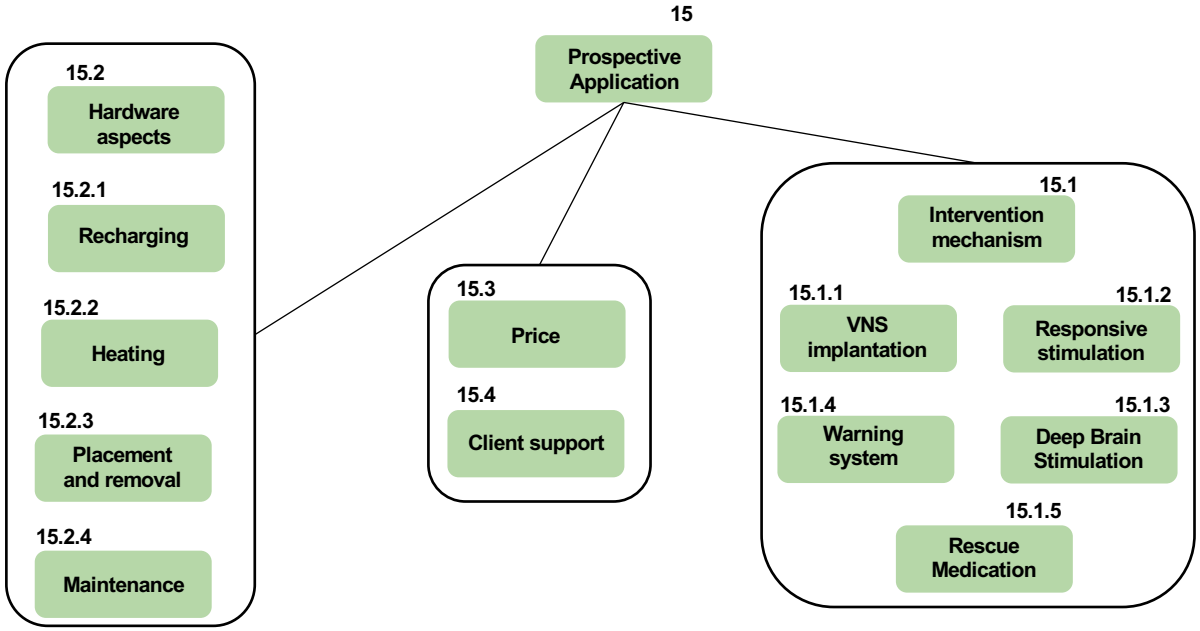
# Prospective Application

A prospective application has an intervention mechanism (15.1), which could be integrated in a closed-loop system, as is the case of vagus nerve stimulation (15.1.1), responsive cortical stimulation with the RNS® system (15.1.2), or deep brain stimulation (15.1.3). The last was recently approved by the FDA and encompasses two ongoing trials (NCT03900468, NCT02076698). An alternative could be a warning system (15.1.4) designed to minimize seizure consequences and/or taking seizure rescue medication, as benzodiazepines (15.1.5). Selecting an adequate intervention strategy is a complex task and must account for patient complacency and consequences (16→15).

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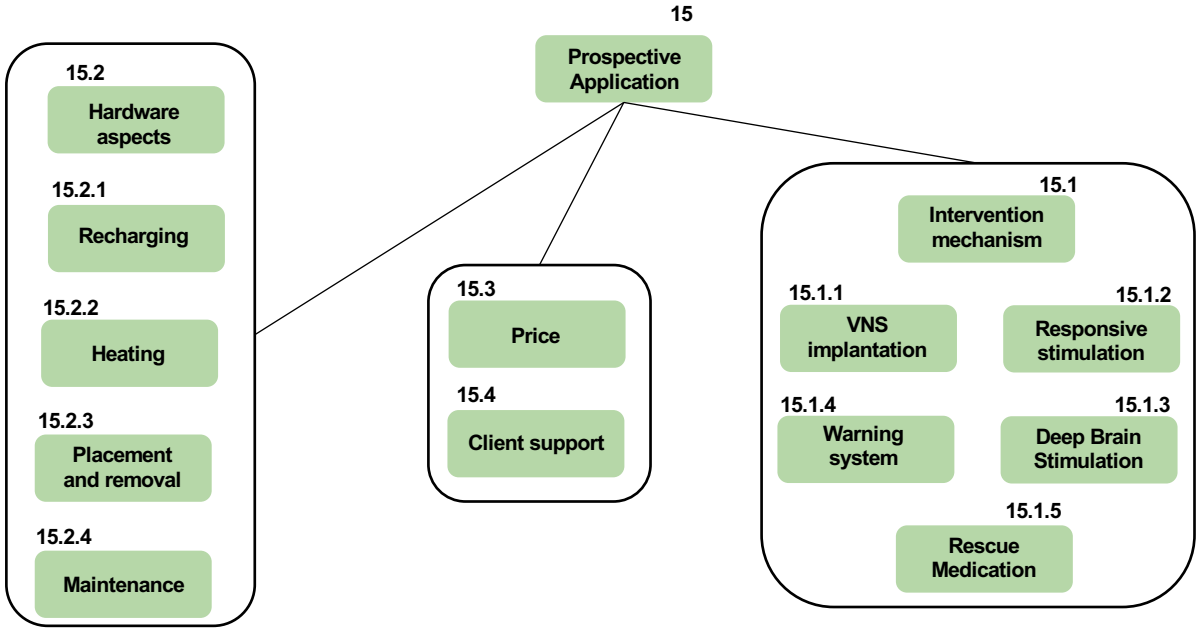
# Prospective Application

Device manufacturers must obey to industry standards and regulations (17→15) related to hardware safety aspects (15.2), such as recharging and low-energy consumption (15.2.1), heating (15.2.2), placement and removal (15.2.3), and maintenance (15.2.4). Others that are equally important concern an affordable price (15.3) and permanent client support (15.4). Consequently, the design of the models should consider the use of fast processing methods allowing its integration in small devices (17.1). It is important to mention that considerable advances have been made in these devices, which is the case of IBM's neuromorphic TrueNorth chip that already allows for deployment of deep learning models.

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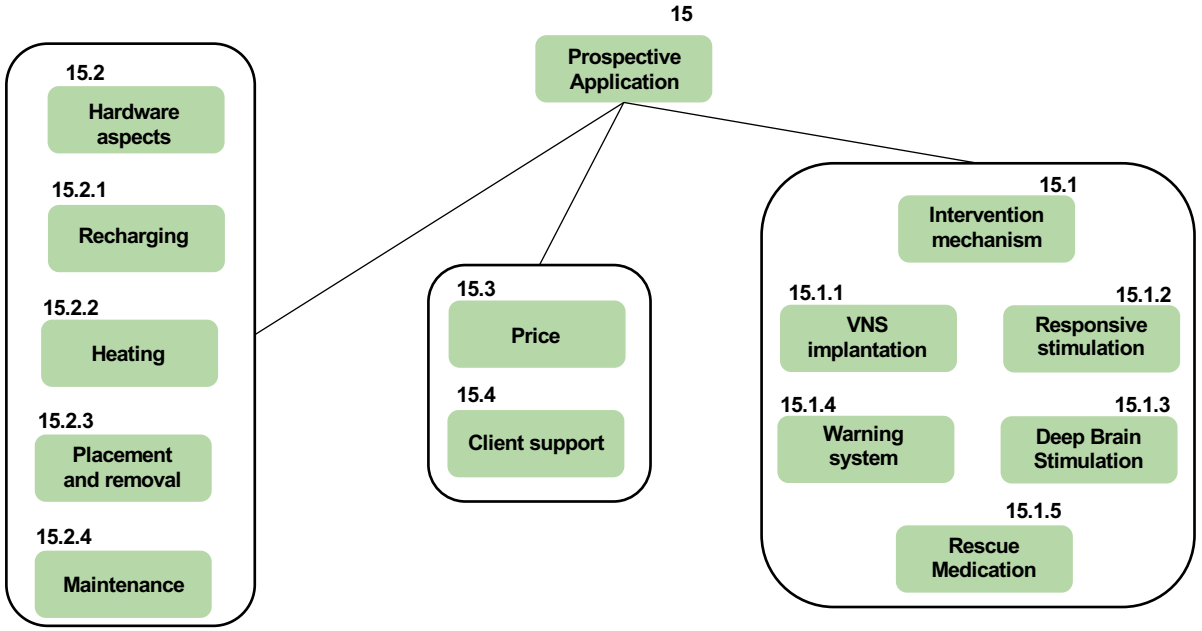
# Prospective Application

In fact, the price may be fundamental to the industry. Electrostimulation by implanting iEEG electrodes is currently considered the most promising strategy, as both RNS® system and Neurovista's system used iEEG. However, these may demand higher human and monetary resources than pre-surgical scalp EEG monitoring, which is already inaccessible to a large part of DRE patients.

In the USA for example, fewer than 1% of DRE patients are examined by a multidisciplinary epilepsy team. Besides, several only have access to level 3 or 4 epilepsy centres many years after onset, often too late to prevent irreversible damage caused by seizures. Thus, by focusing immediate efforts on low-cost and accessible warning systems followed by rescue medication intake instead, we may reach considerably more DRE patients.

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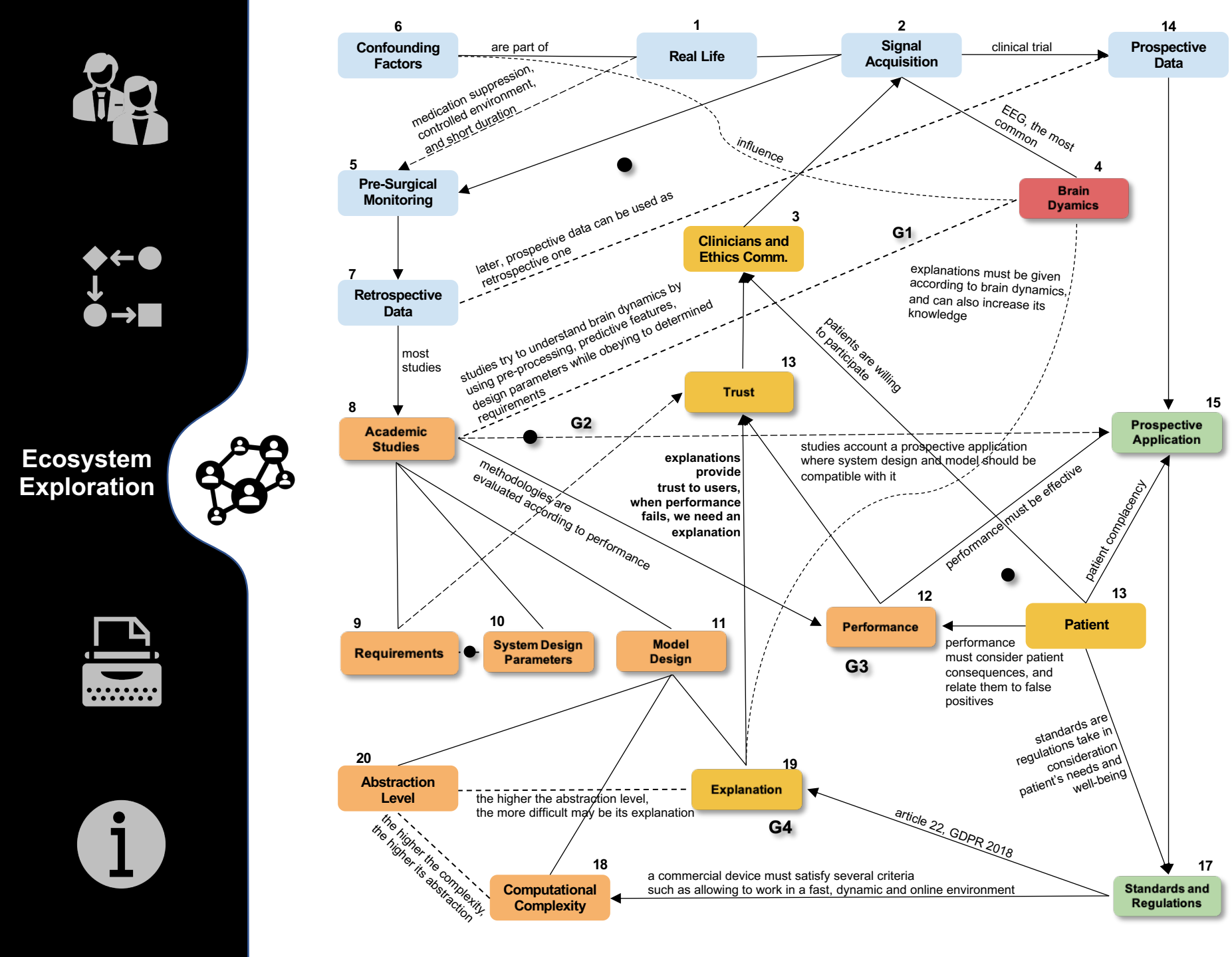
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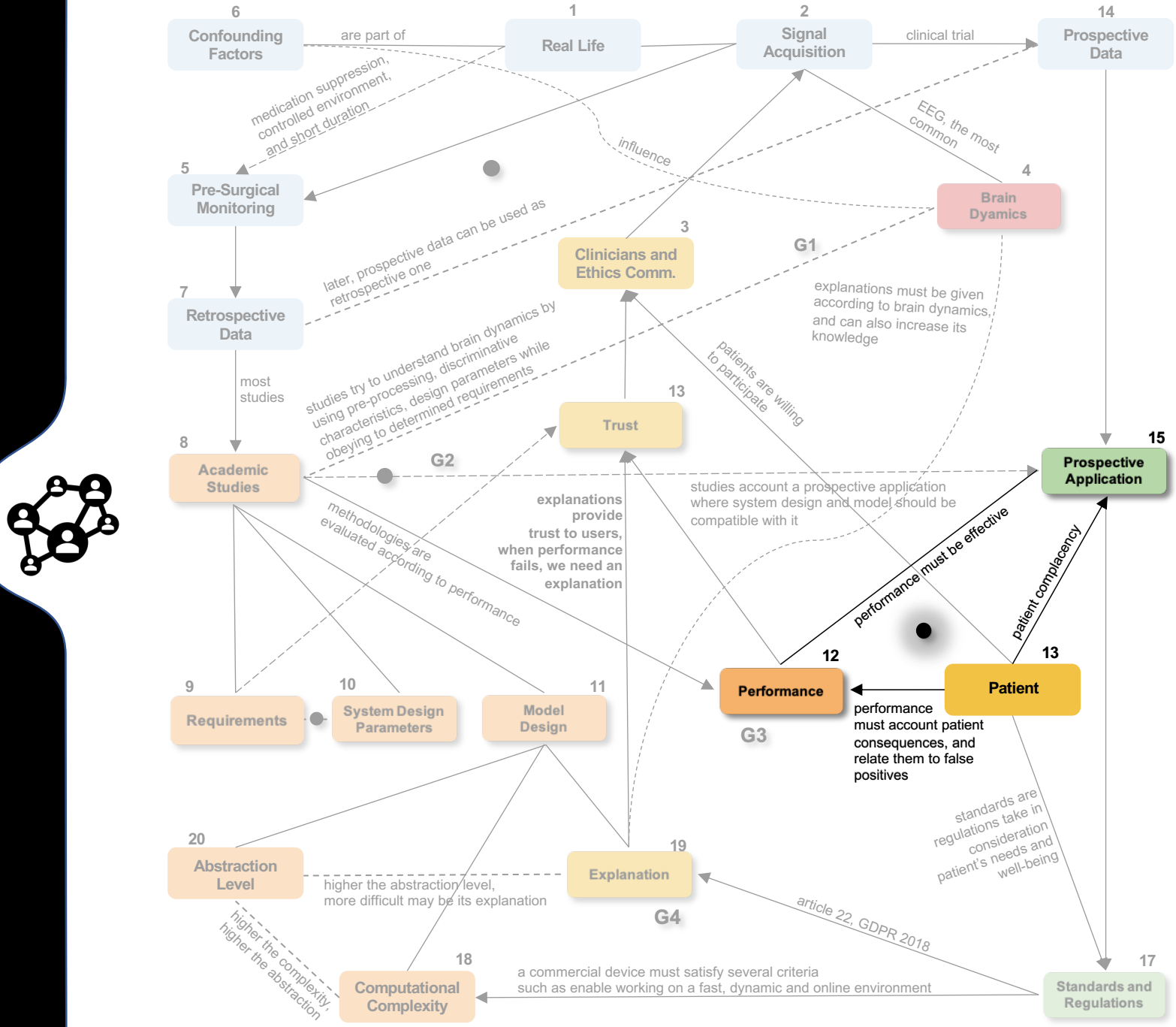
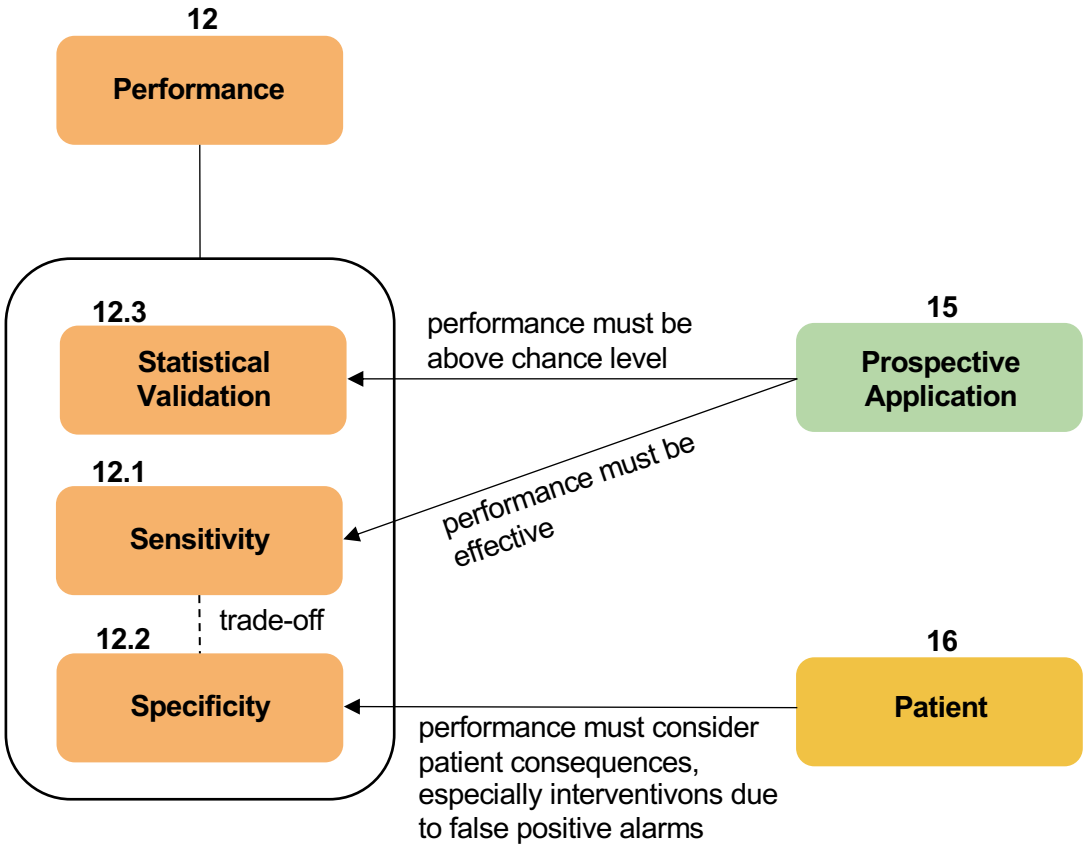


# Relations between Performance, Prospective Applications, and Patient

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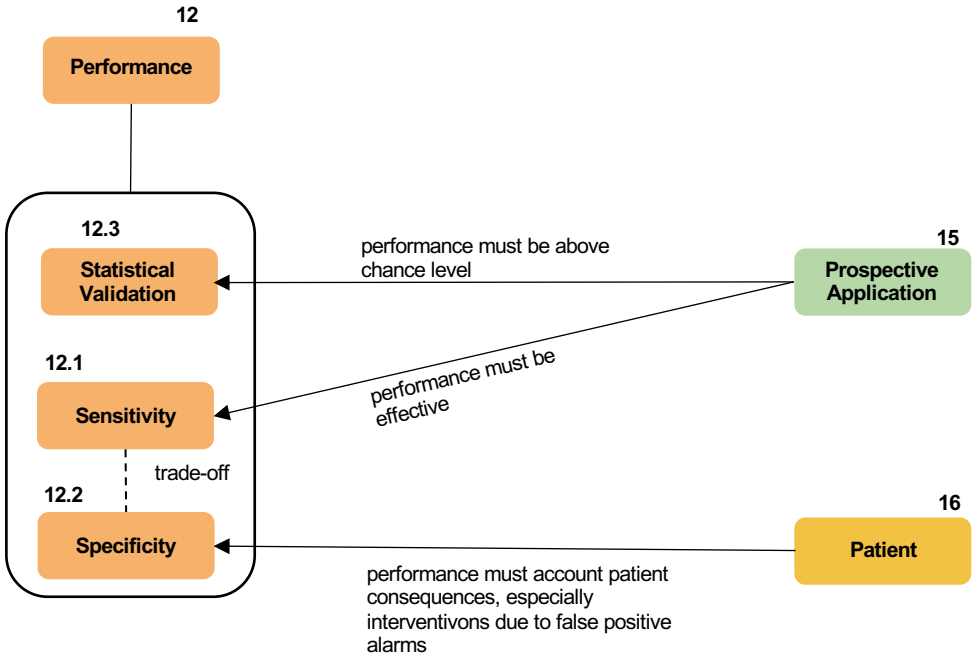
# Relations between Performance, Prospective Application, and Patient

Some researchers suggest presenting an overall performance by computing the area under the receiver operating characteristic curve (relating sensitivity and specificity) [14, 33]. However, the results can be interpreted according to the envisioned clinical application, specifically by considering intervention consequences for patients (16→12.2). For instance, when considering the use of a warning system during pre-surgical monitoring, a maximum value of 0.15 FPR/h [8, 33] has been considered as the upper limit of false alarms that cause bearable/tolerable levels of stress and anxiety.

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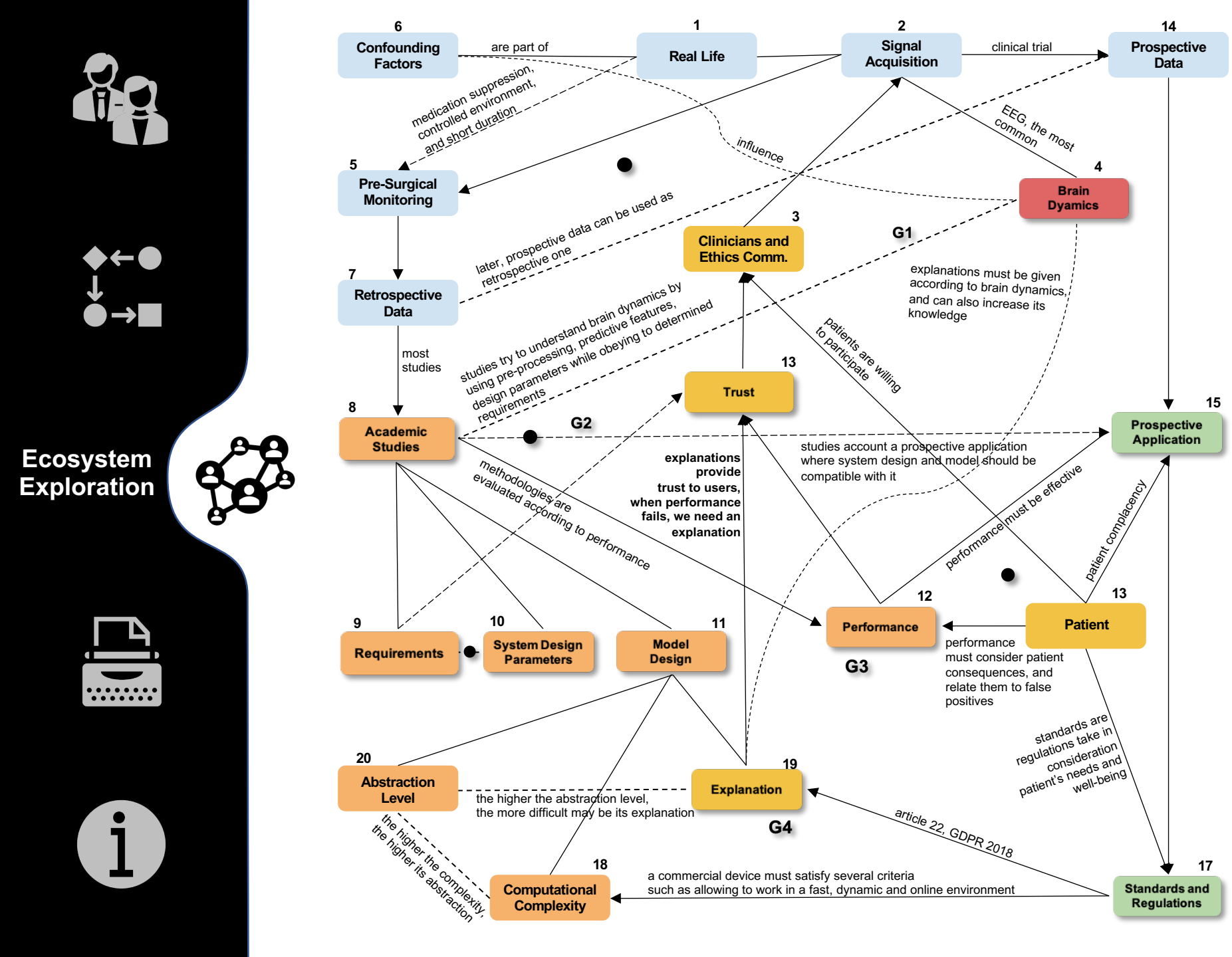
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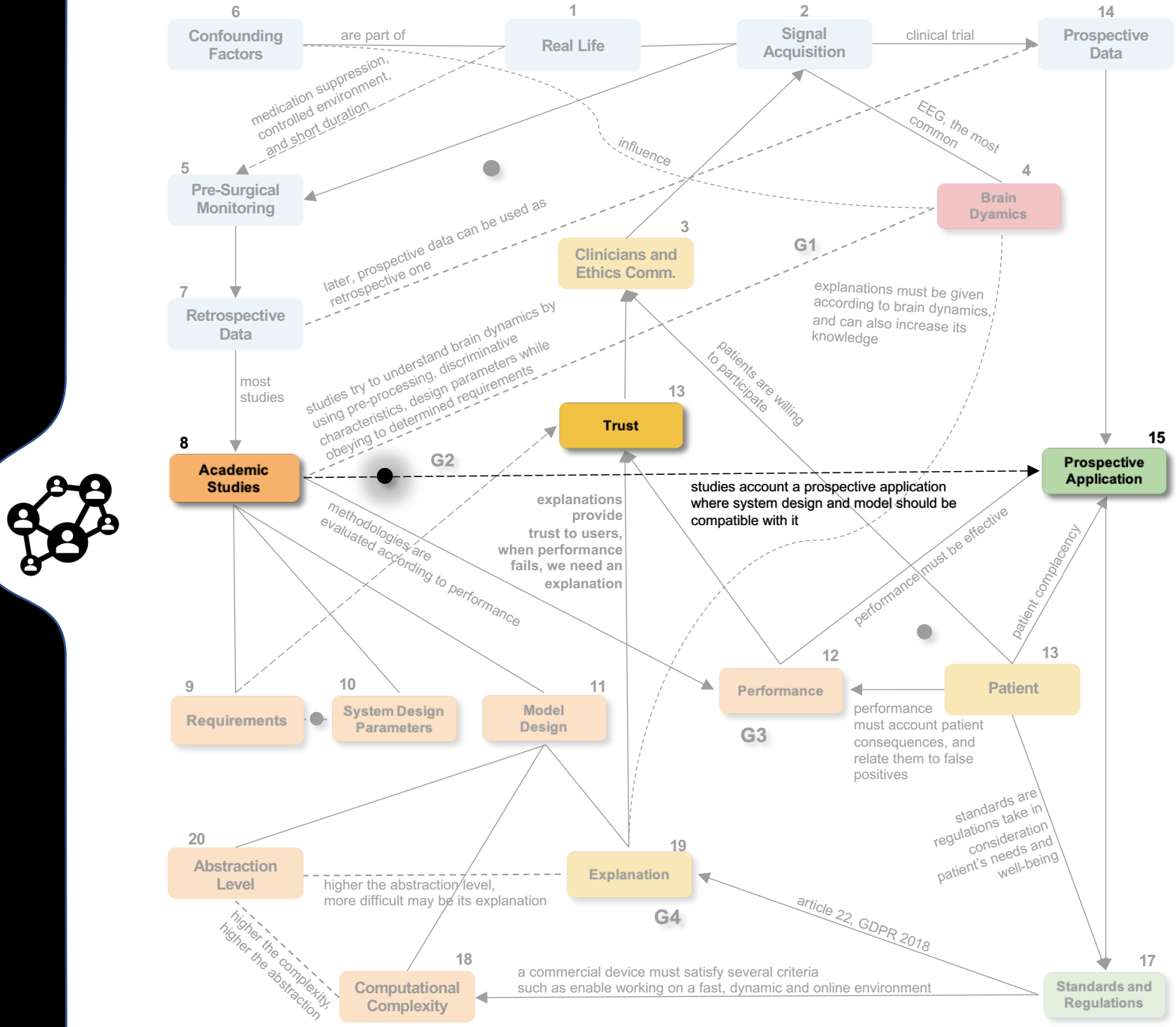
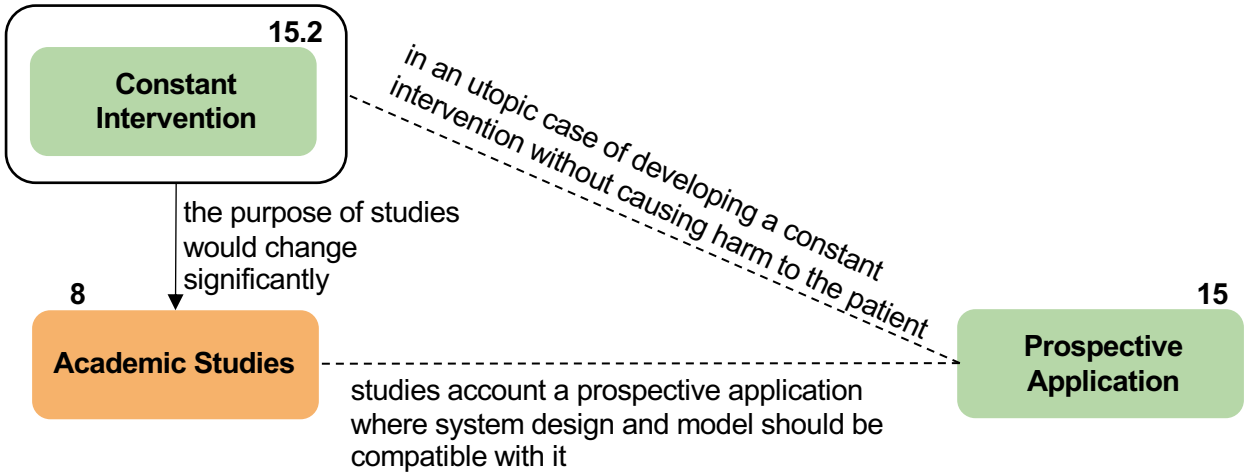


# Relation between Prospective Application and Academic Studies

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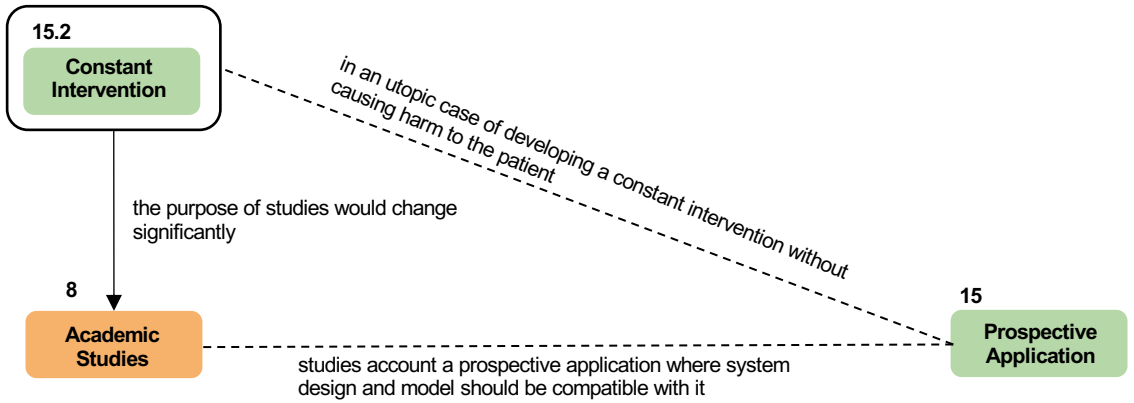
# Relation between Prospective Applications and Academic Studies

Ideally, studies envision and open the way to the development of potential prospective applications (8- -15). Thus, a study must emulate a real life scenario.

It is interesting to reflect on the ideal scenario. The development of a constant and effective intervention (15.2), such as chronic or scheduled stimulation from implantable devices, without any side effects (stress and anxiety, long exposure to medication) and device-related problems (infection, intracranial haemorrhage, tissue reaction, skin erosion, lead migration, among others) would change the paradigm. Academic prediction studies would just focus on increasing knowledge on brain dynamics (15.2→8) as there was no need to investigate another prospective application. Given the amount of today's limitations, this may be utopic. However, we find it relevant to stress the purpose of seizure prediction research.

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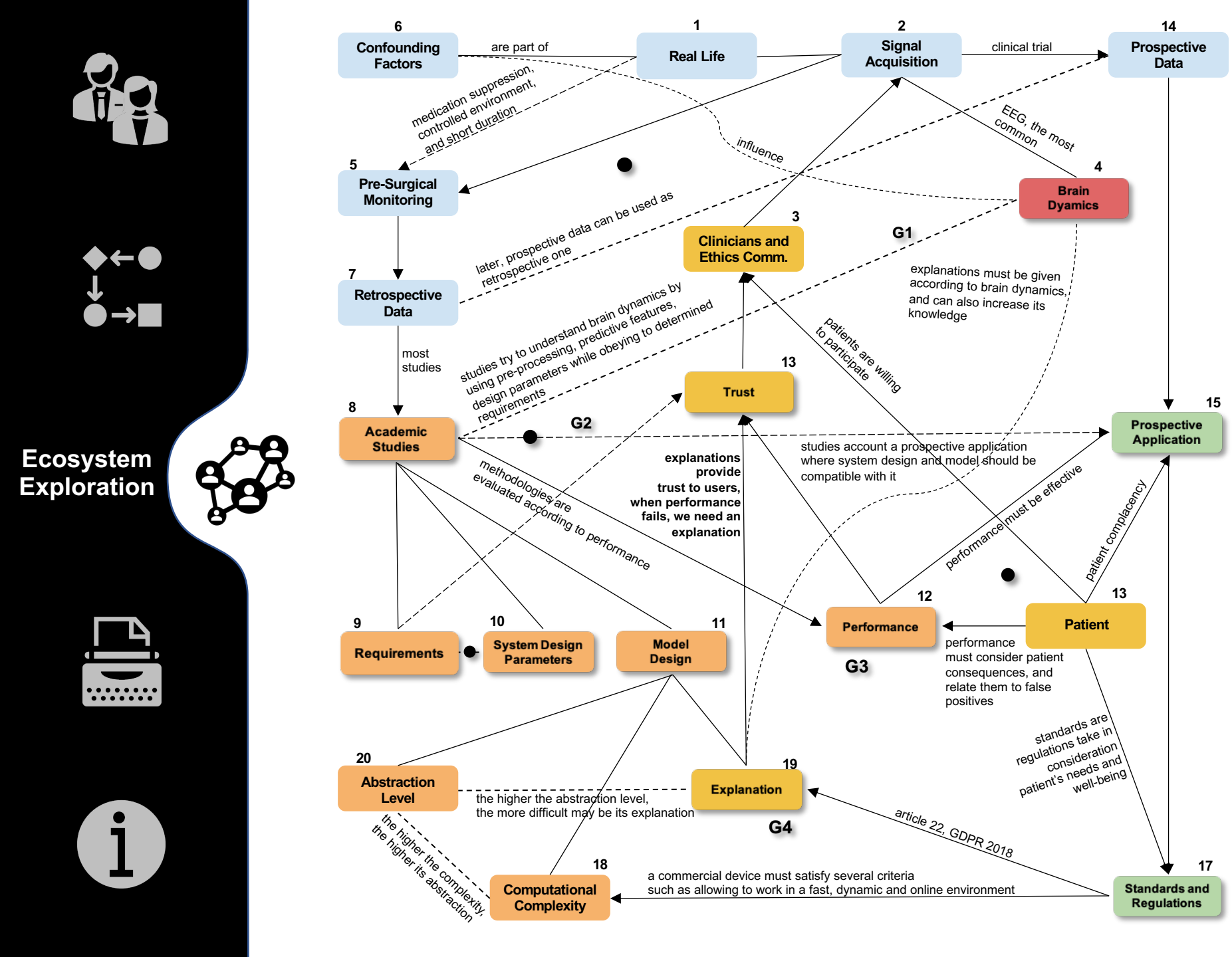
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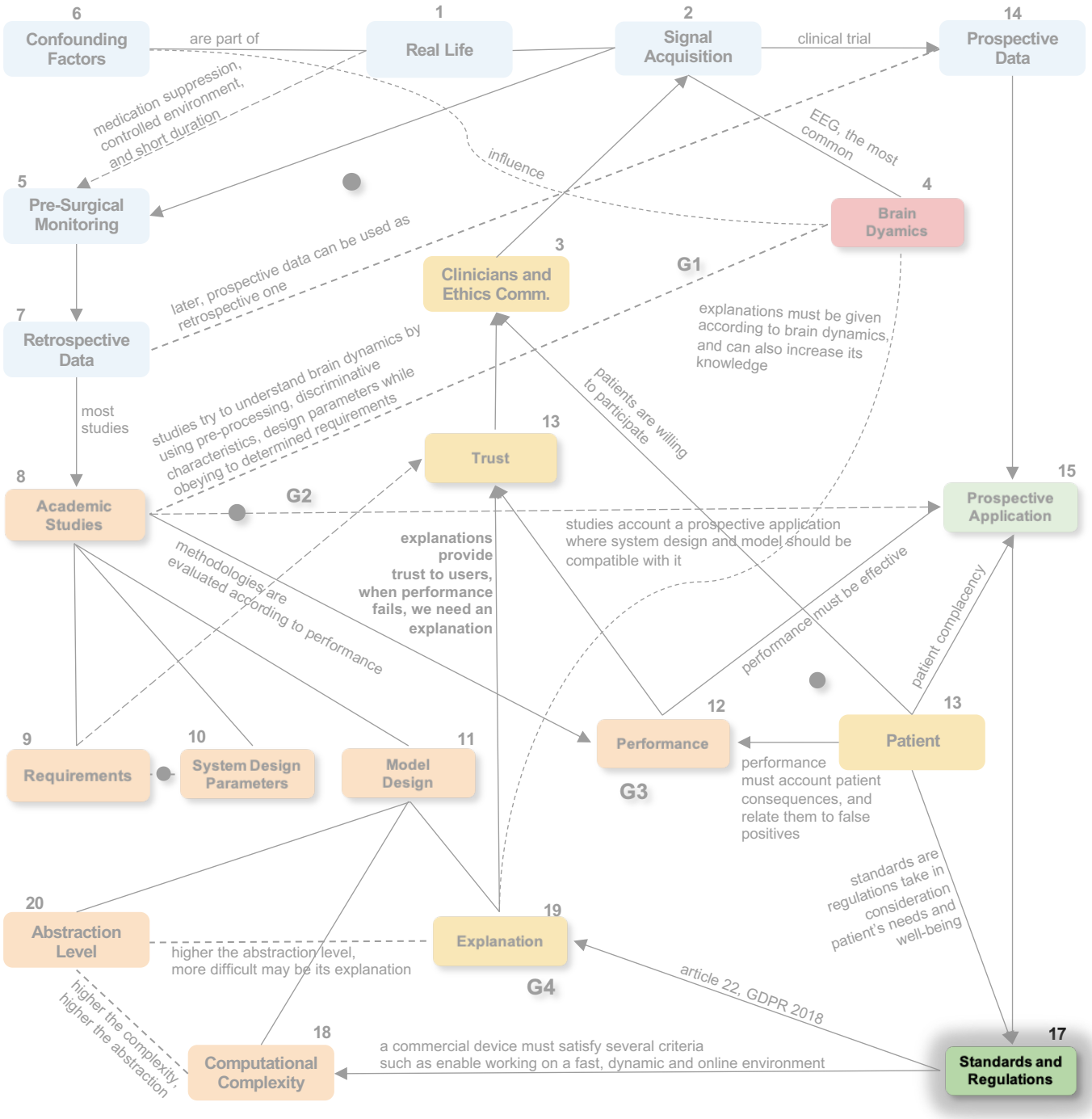
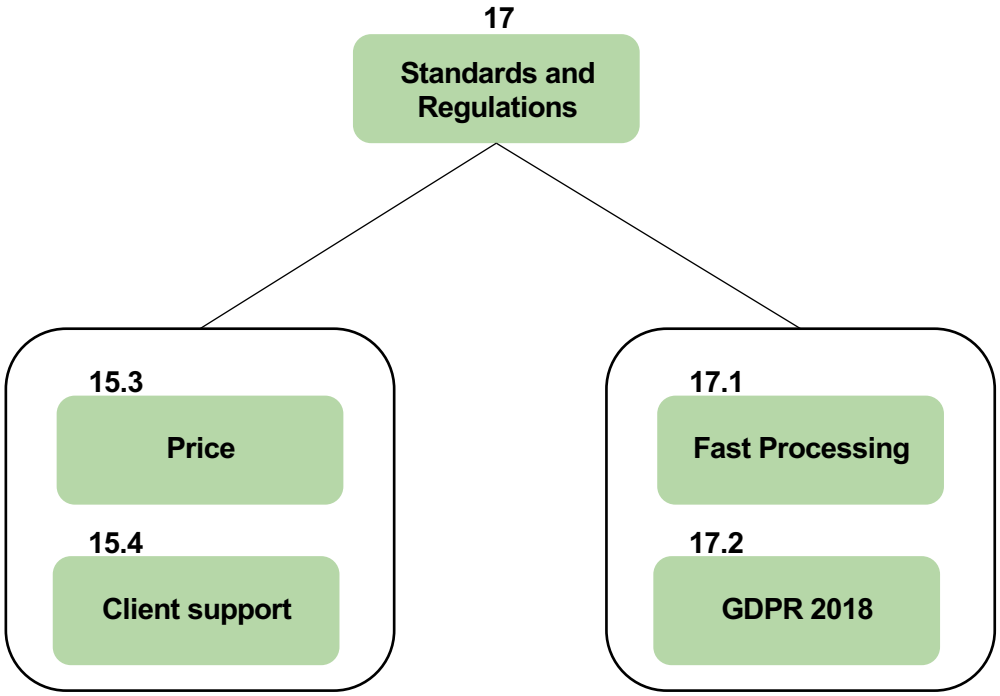


# Encapsulation of Standards and Regulations

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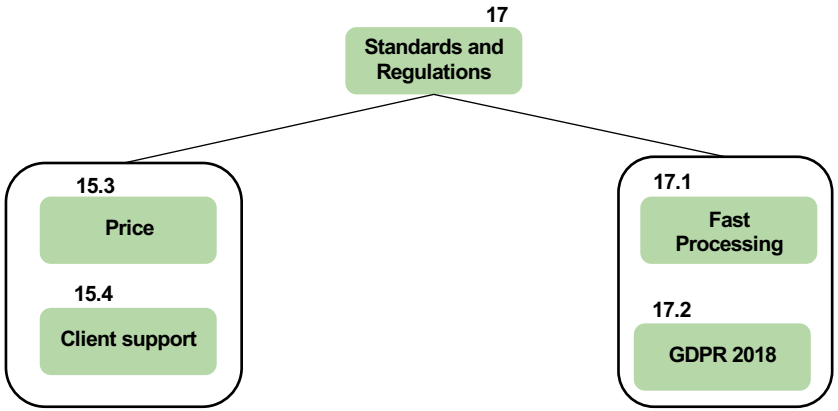
# Standards and Regulations

Device manufacturers must obey to industry standards and regulations (17→15) related to hardware safety aspects (15.2), such as recharging and low-energy consumption (15.2.1), heating (15.2.2), placement and removal (15.2.3), and maintenance (15.2.4). Others that are equally important concern an affordable price (15.3) and permanent client support (15.4). Consequently, the design of the models should consider the use of fast processing methods allowing its integration in small devices (17.1). It is important to mention that considerable advances have been made in these devices, which is the case of IBM's neuromorphic TrueNorth chip that already allows for deployment of deep learning models.

The 2018 GDPR (17.2), for European citizens and European economic space, is also an important aspect. Article 22 presents the first steps towards legislation on algorithm explainability for high-risk decisions based on personal data (17→19). Summarily, standards and regulations concern patient safety, needs and well-being, which guarantees best practices (16→17).

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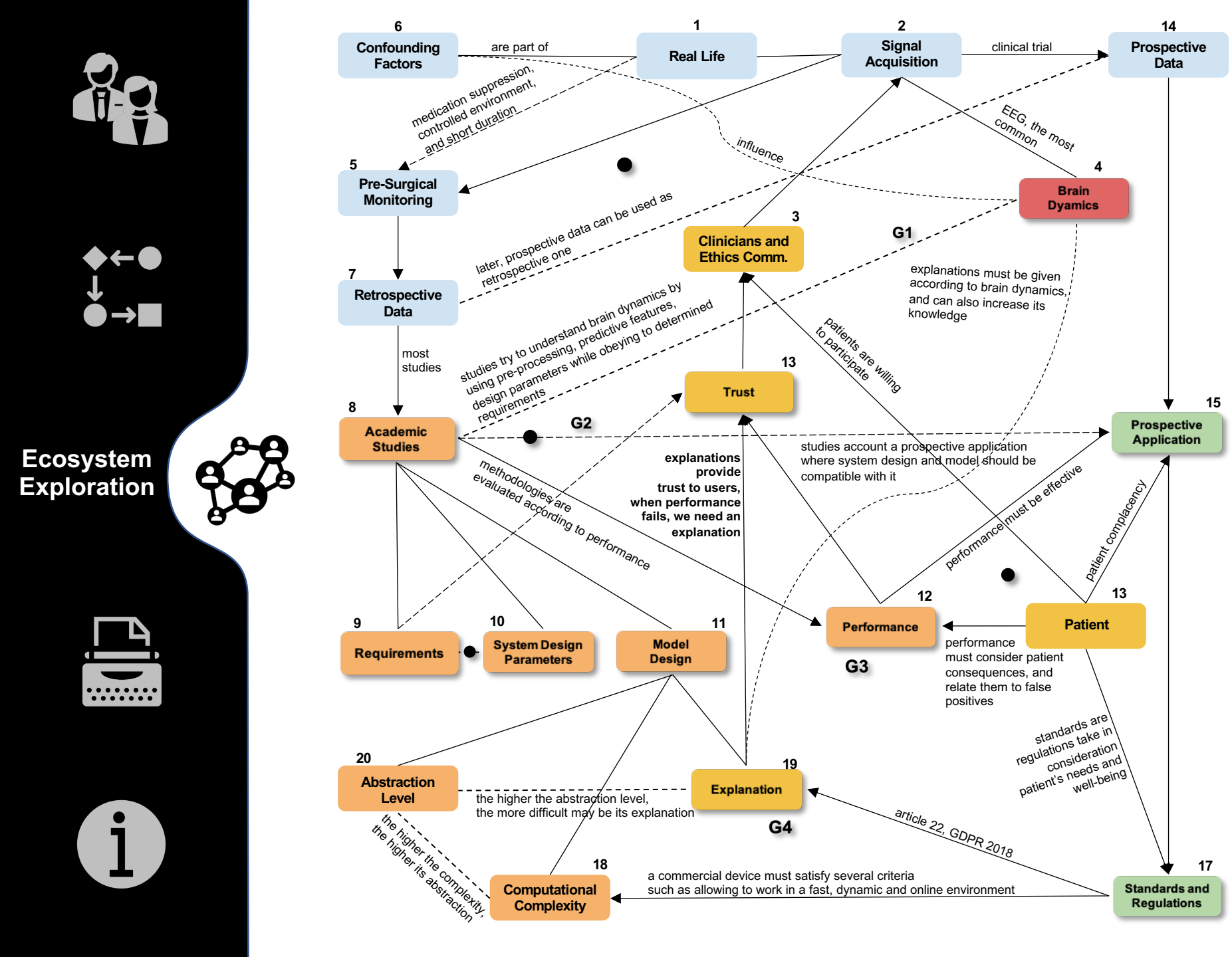
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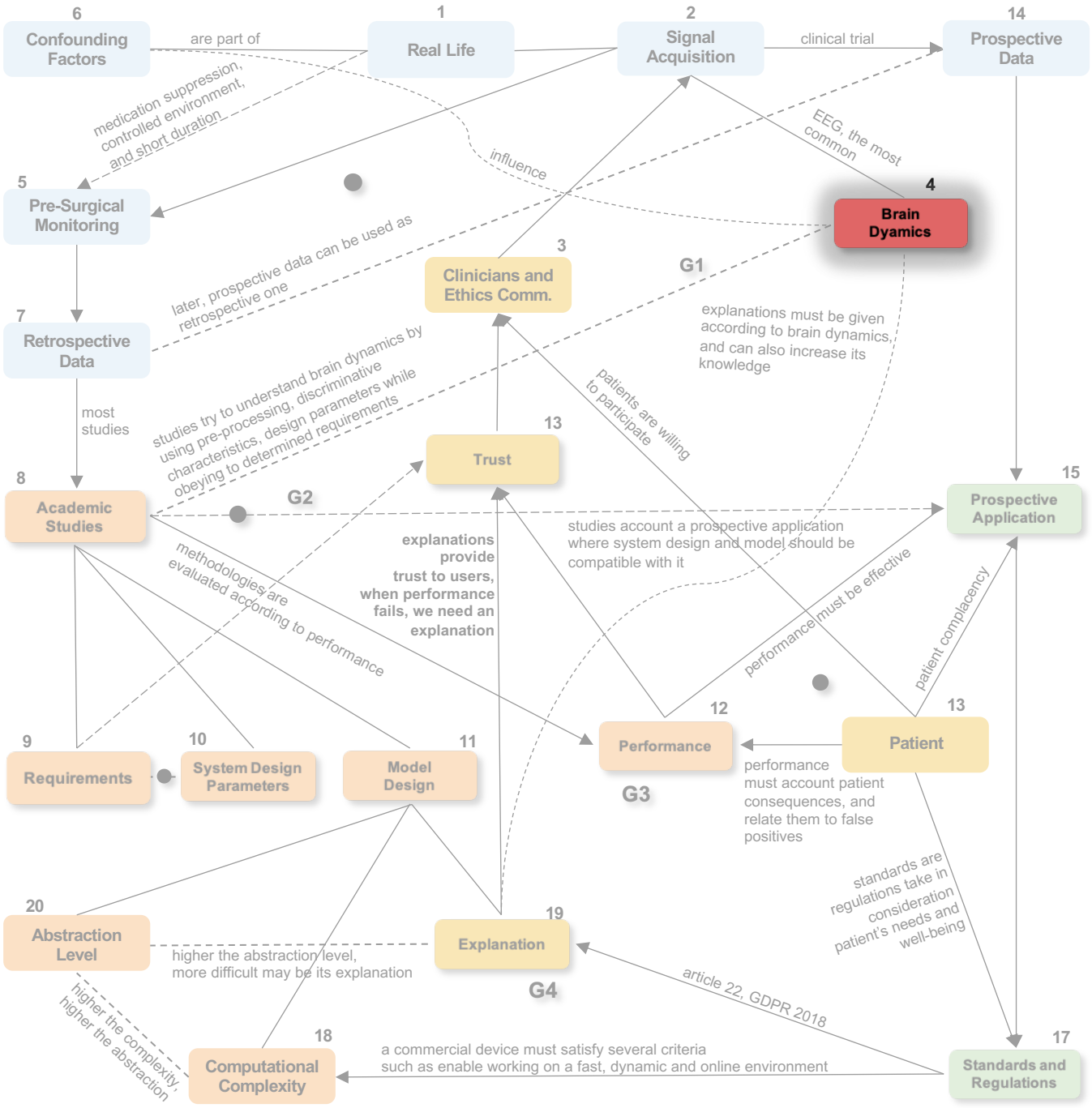
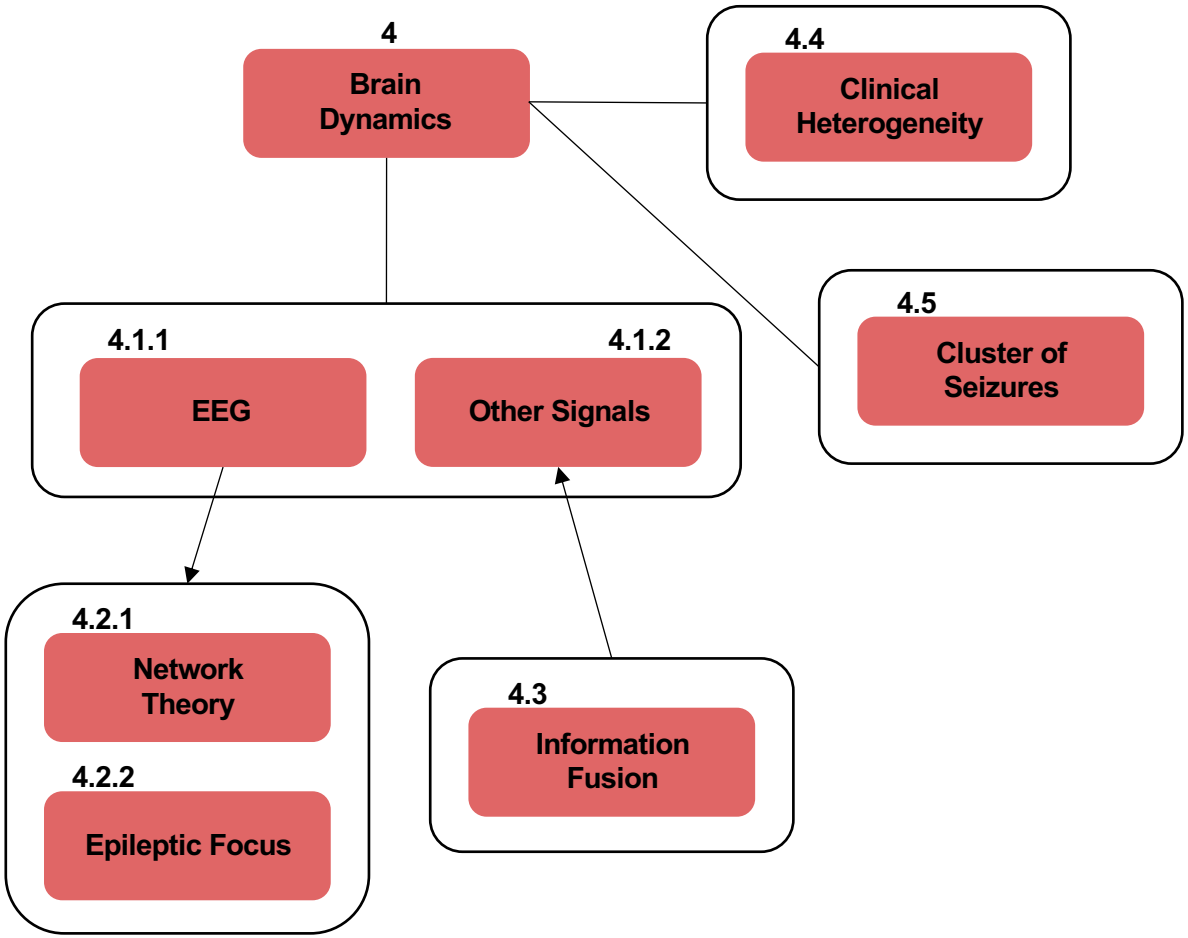


# Encapsulation of Brain Dynamics

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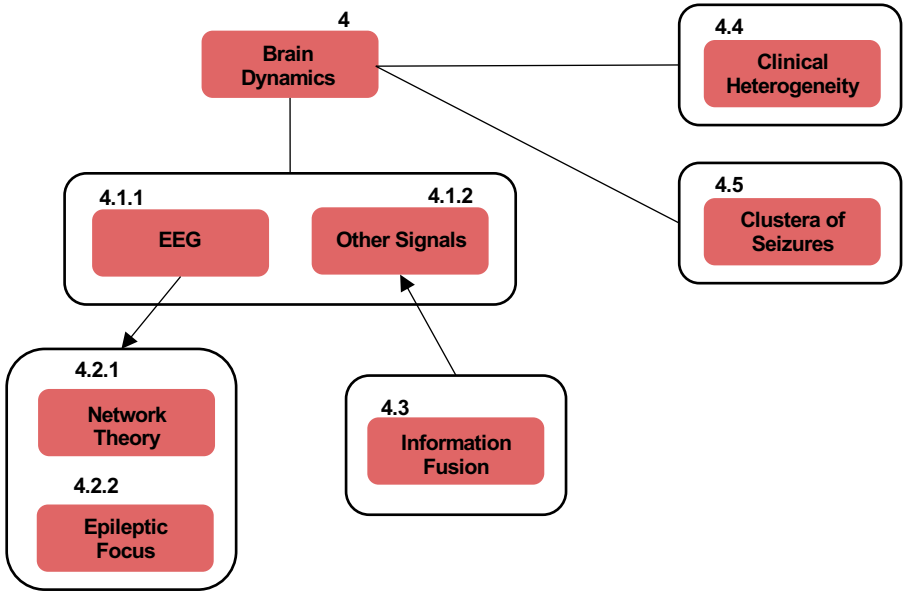
# Brain Dynamics

Brain dynamics (4) play a fundamental role in predicting seizures. Ictogenesis is known for leading to a hyperexcitability state that increases brain synchronization. Thus, the EEG (4.1.1) is the most used signal. It can be acquired using scalp or intracranial (iEEG) electrodes, each one addressing different assumptions on brain dynamics and therefore being more compatible with specific applications.

Scalp EEG obtains electrical activity from all surface regions, which is more suitable for handling the network theory (4.2.1). The latter proposes that seizures may arise from abnormal activity that results from a large-scale functional network and spans across lobes and hemispheres. Still, scalp EEG requires significant patient complacency as they cause stigma and discomfort. One can also expect frequent signal artefacts and noise. Its intervention application could be a warning system to reduce seizure consequences, which may be the most affordable option and, therefore, the one that requires fewer resources.

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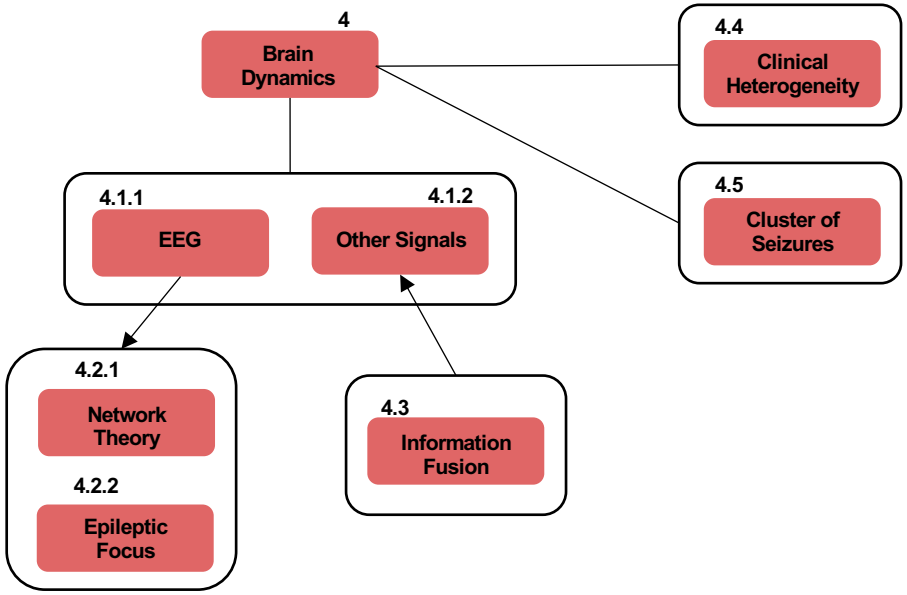
# Brain Dynamics

Despite iEEG has a higher signal-to-noise ratio and can be used to develop closed-loop intervention systems, patients may suffer from haemorrhage, device movement or infection, among others. Authors commonly focus on brain activity belonging to a given region, generally the epileptic focus (4.2.2). In fact, authors assume it is possible to predict seizures by only inspecting the epileptogenic area. Furthermore, the SeizeIT2 clinical trial also explores EEG behind-the-ear that brings higher patient comfort, and Debener et al. developed an EEG-ear array which demonstrated feasibility for long-term recordings.

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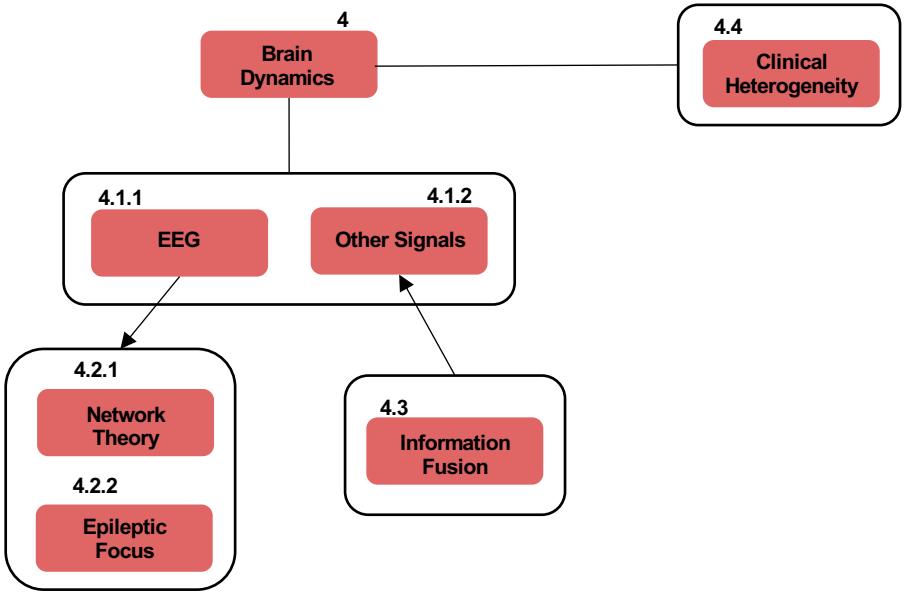
# Brain Dynamics

Other sources of information (4.1.2) can be used to explore changes in brain dynamics (e.g., MRI) and also alterations in other non-neurological physiological parameters occurring during pre-ictal interval. For example, the cardiovascular dynamics regulated by the autonomous nervous system can be captured by the electrocardiogram and has been proven to carry complementary information for seizure prediction. Hence the growing belief that the analysis of multimodal data may provide improved results. In fact, multiple confirmations that the same dynamics may be present at different scales and biosignals (4.3) might enhance explainability and therefore, increase trust (19→13), as mentioned in the following sections.

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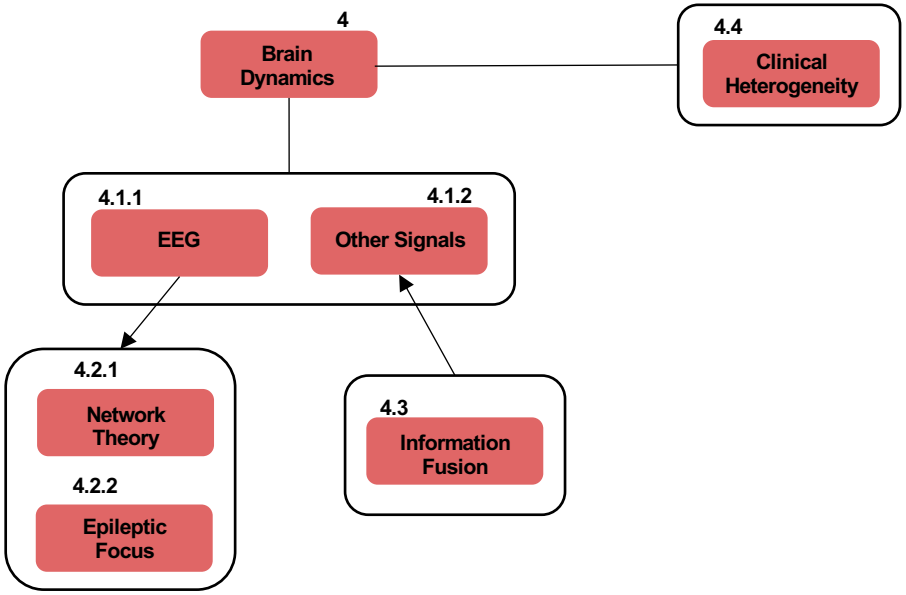
# Brain Dynamics

Moreover, the large clinical heterogeneity associated with epilepsy (4.4) also promotes current research directed at deepening understanding of this disease. There are several types of epilepsy syndromes, characterized by different types of epilepsy. Clinicians distinguish epilepsy types according to the types of seizures, clinical history, EEG data and imaging features. Furthermore, several co-morbidities may arise, such as intellectual and psychiatric dysfunction. Seizure generating mechanisms are specific for each patient and each type of seizure, even though the source of spiking activity, for example, still remains unclear. Additionally, it has been suggested that brain hyperexcitability induces a time dependency on seizures that leads to the occurrence of clusters of seizures (4.5). This aspect turns the ictogenesis process more complex and difficult to understand.

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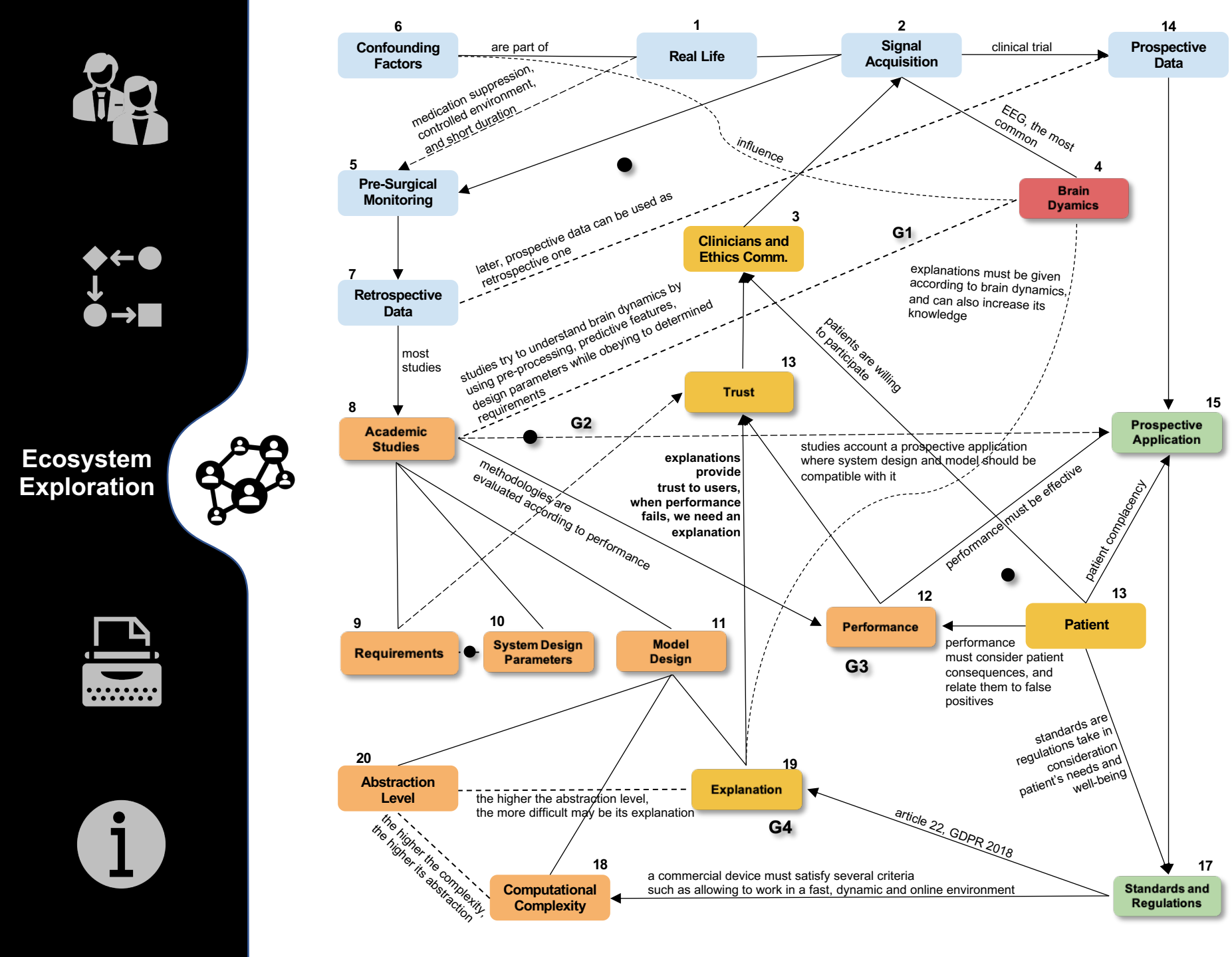
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# Patient

Our greatest limitation was the patient role, as we did not properly include his/her agency. We strongly believe that we (the academic community) are still far from understanding what is it like to be a patient: the patients' expectations are largely different than the ones from clinicians and data scientists. In the future, we need to be more aware of the active role that a patient can have.

The case of Dana Lewis and Hugo Campos are clear examples, where the patients might be able to track their data, analyze it and therefore, better control their closed-loop systems. Dana Lewis created the “Do-It-Yourself Pancreas System” (#DIYPS), founded the open-source artificial pancreas system movement (#OpenAPS), and advocates patient-centred, -driven, and -designed research. She created #DIYPS to make her continuous glucose monitor (CGM) alarms louder, and developed predictive algorithms to timely forecast necessary actions in the future (https://diyps.org/about/dana-lewis/).

Hugo Campos was diagnosed with hypertrophic cardiomyopathy: a disease in which the heart muscle becomes abnormally thick and that can be fatal. He received an implantable defibrillator, which is a device that electrostimulates the heart in case of dangerous arrhythmias. Simply put, after losing his health insurance, he bought a pacemaker programmer on eBay and learned how to use it with a two-week course. Hugo Campos is now a data liberation advocate and leader in the e-patient movement (https://medicinex.stanford.edu/citizen-campos/).

In fact, article 22 of GDPR 2018 not only provides patients with the right to have an explanation for any algorithm decision but also gives them the right to question those decisions.

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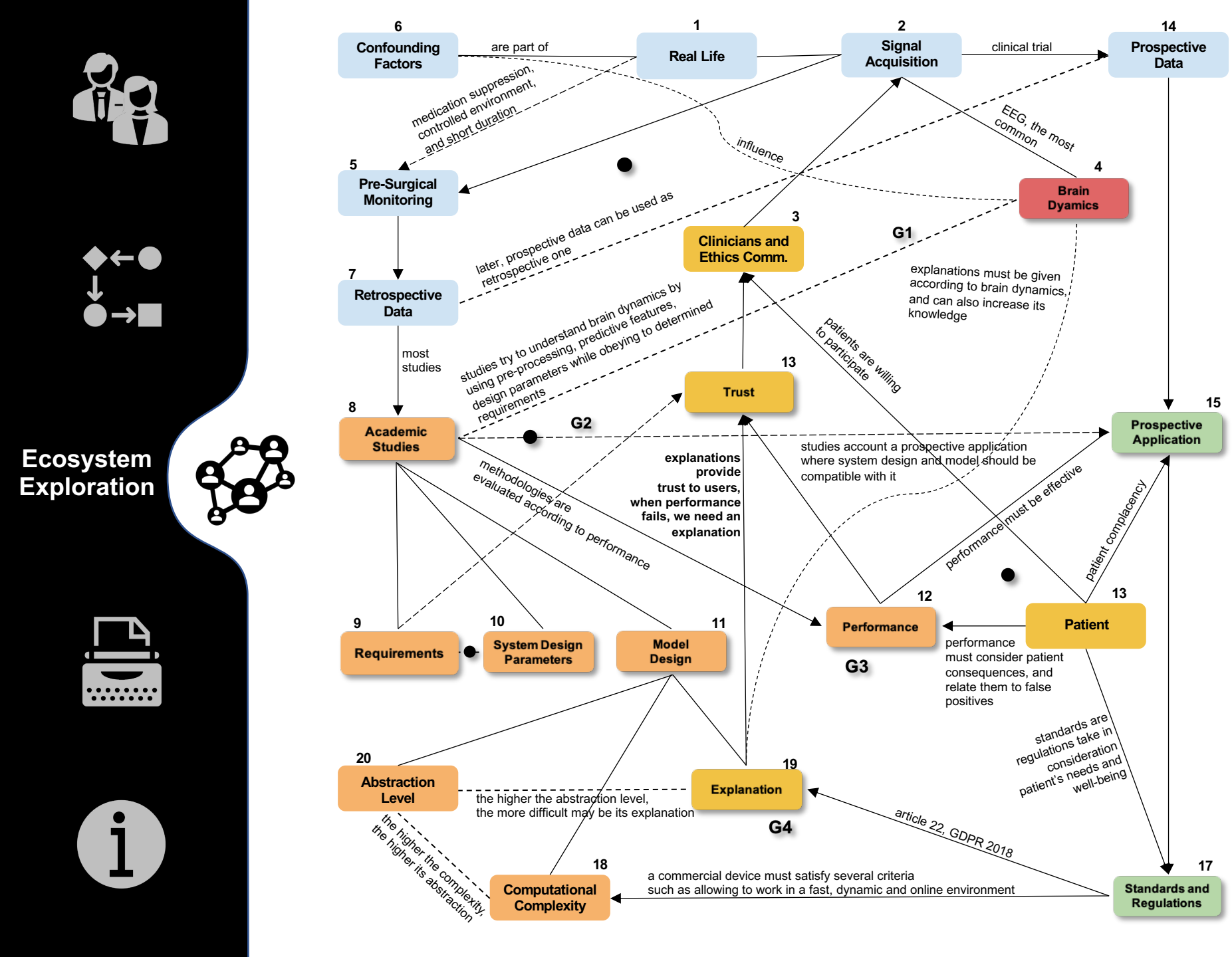
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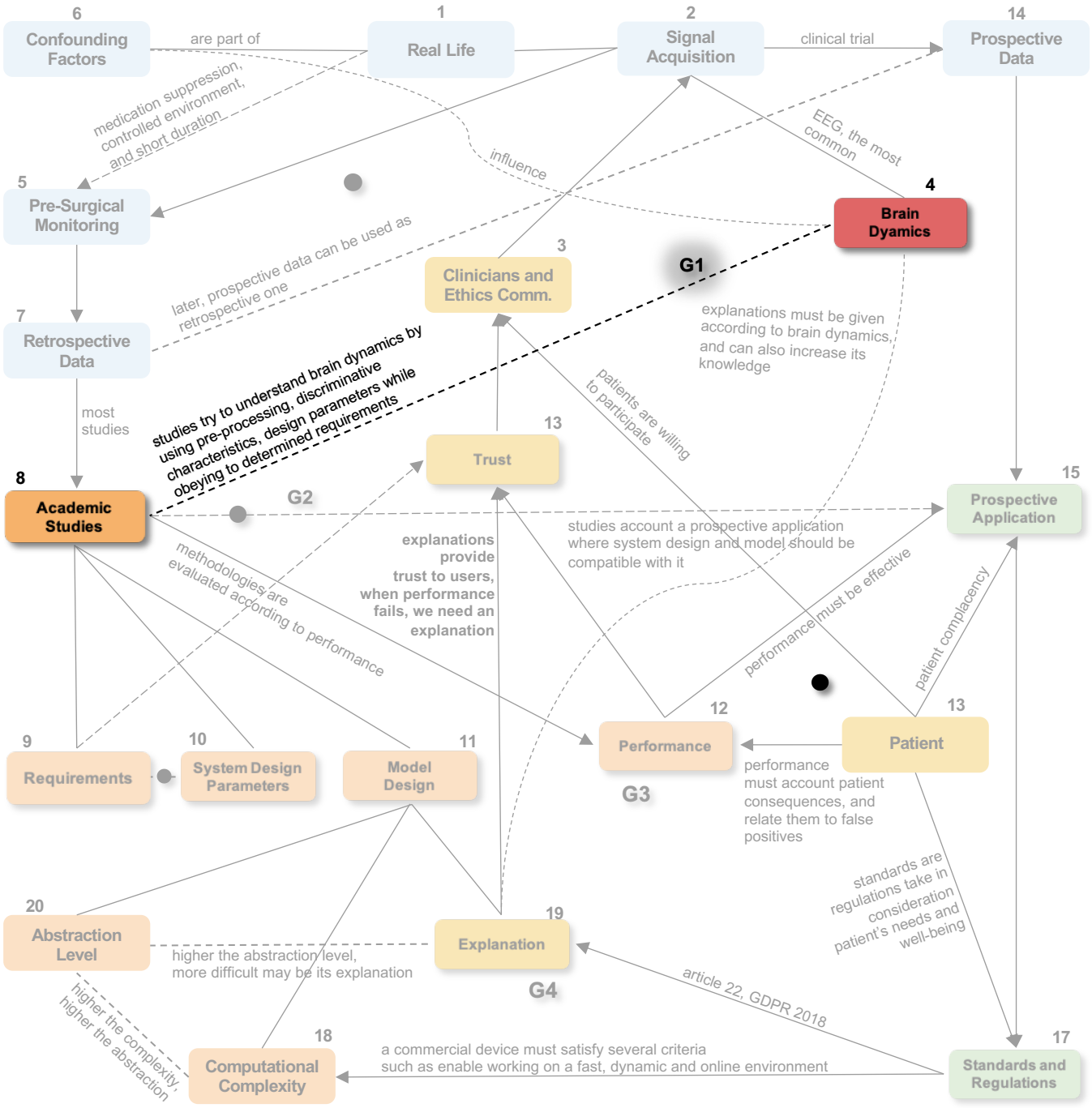
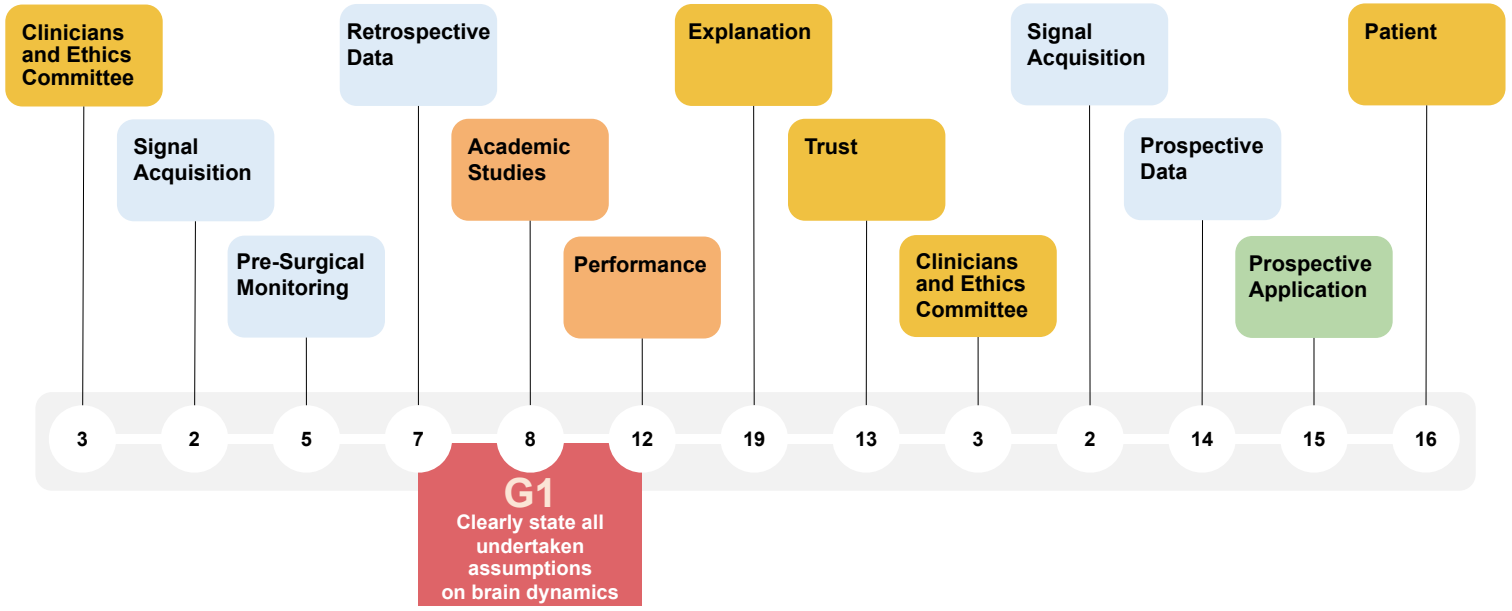


# Guideline 1

G1 concerns undertaken assumptions on brain dynamics, which differ between studies due to available data and used methodology. Authors should state their assumptions regarding brain dynamics before presenting the mathematical tools used in data analysis. Experienced researchers may understand what is at stake. However, others may benefit from the assumption statement by gaining faster insight, enabling easier comparison among studies, and understanding limitations.

For instance, authors claim that tackling confounding factors increases performance, but believing in a direct causal relation may be naive. Reducing confounding factors does not increase performance *per se* but rather improve the experimental design and study requirements by improving assumed brain dynamics (8- -4), namely in model design and problem definition. Similarly to confounding factors, aspects as problem definition and system design parameters encounter the same problem.

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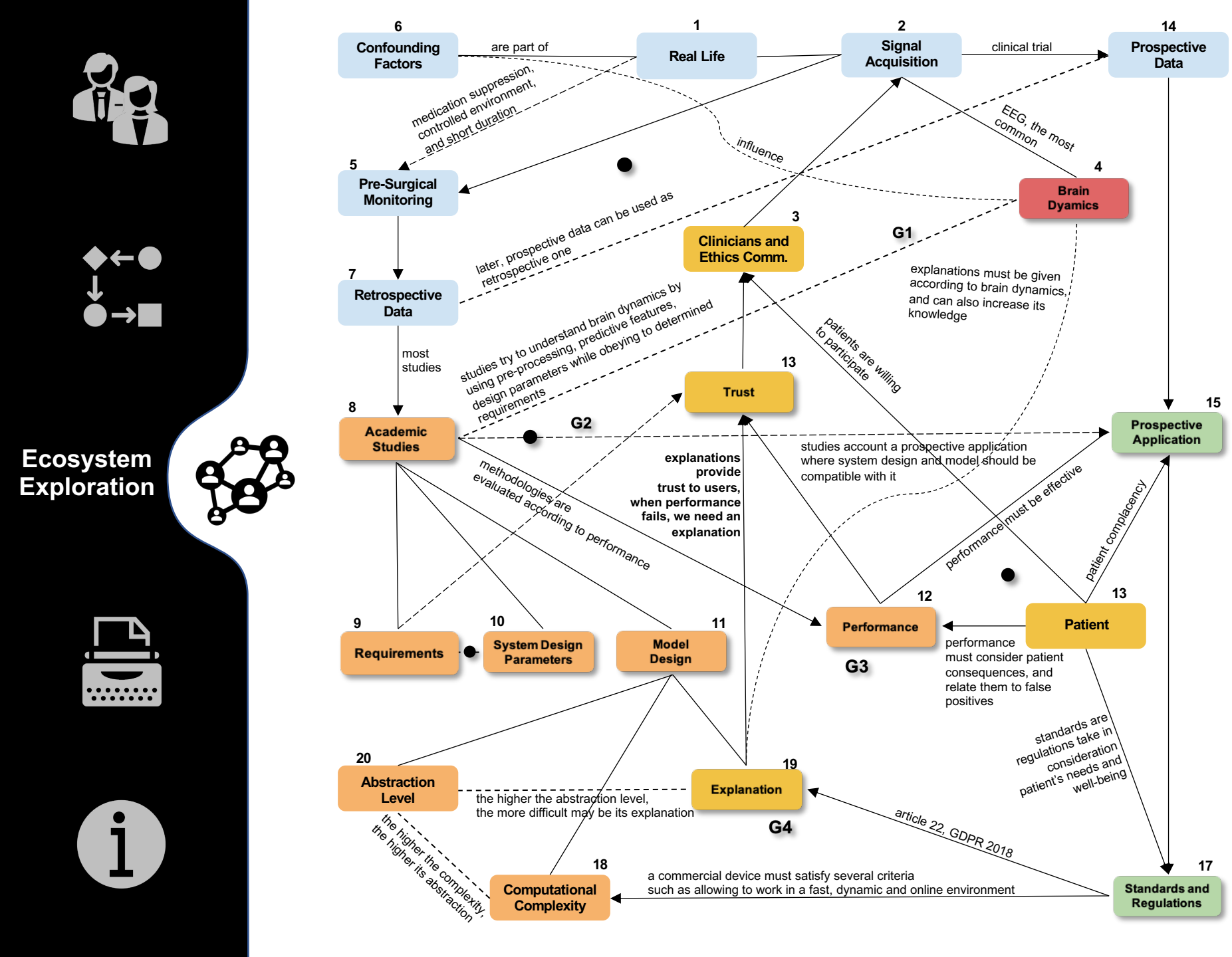
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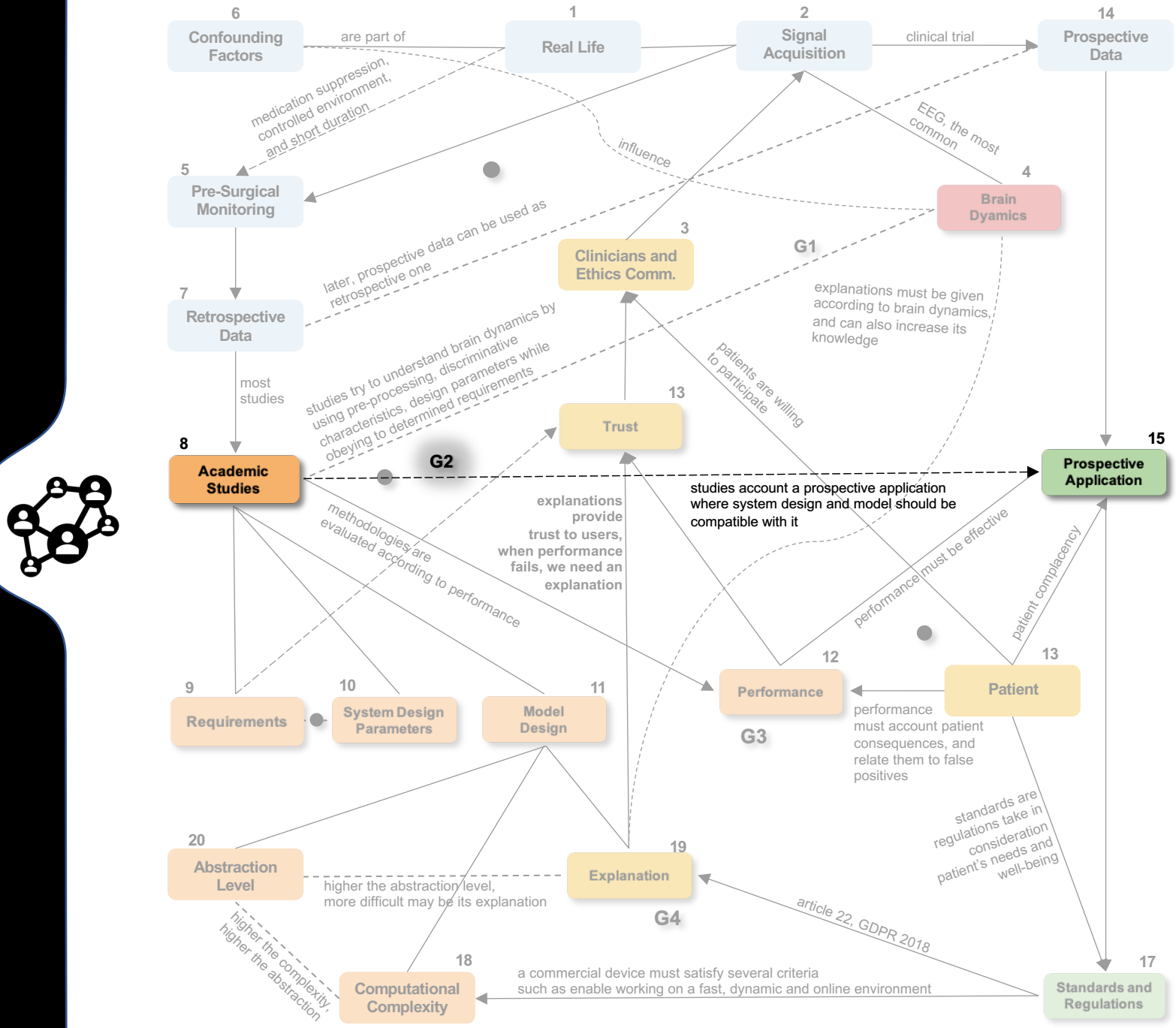
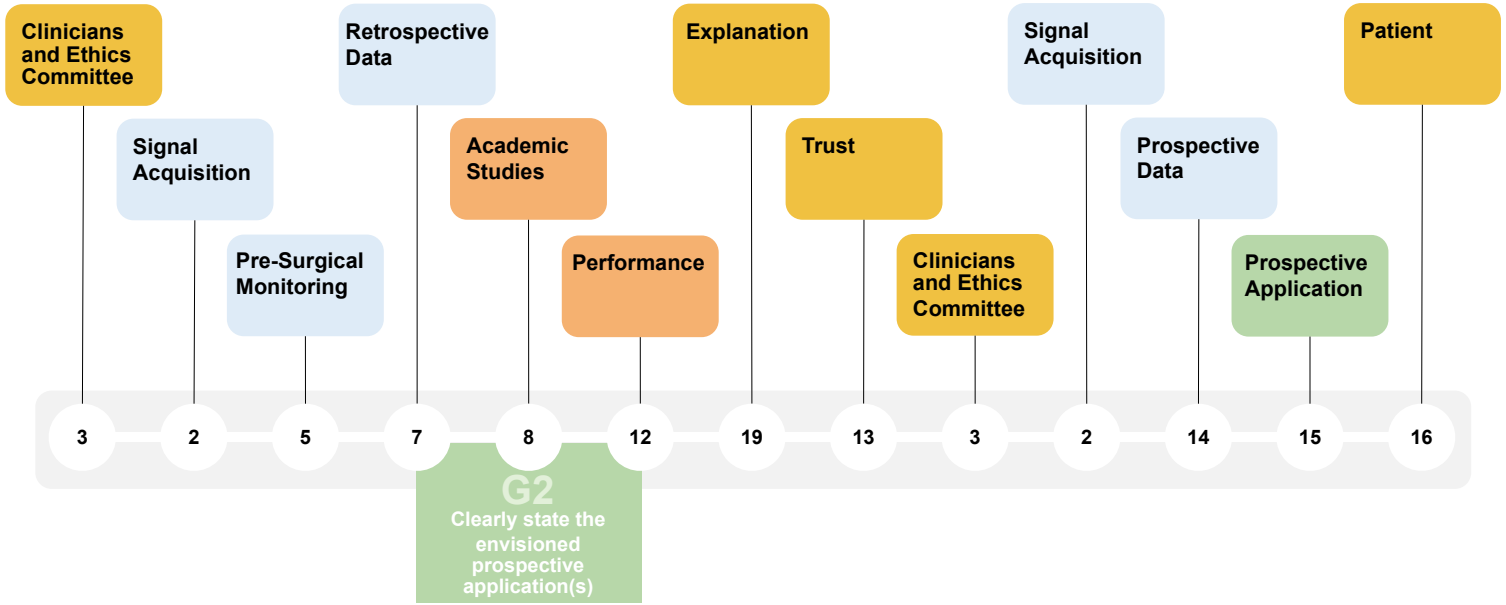


# Guideline 2

G2 concerns stating the prospective applications envisioned with the designed experiment (8- -15). It helps readers and authors understanding what is at stake concerning system parameters, the type of data and envisioned intervention. For instance, most seizure prediction studies report optimal SOP periods for 30-60 minutes. Nevertheless, the RNS® system is programmed to make electrical discharges up to 5000 ms. Possibly, for closed-loop systems, these SOP intervals are too long to deliver an effective intervention. Additionally, many authors use short SPH intervals in scalp EEG studies. In these cases, an SPH of 10 seconds or even 1 minute is not enough for taking action after an alarm, such as reaching a secure place or take rescue medication. For example, diazepam rectal gel (the only FDA drug approved for seizure cluster, and which might be tested as prevention) takes 5-10 minutes to work, while oral diazepam or lorazepam takes 15 minutes. This guideline would stimulate discussion regarding study limitations, as well.

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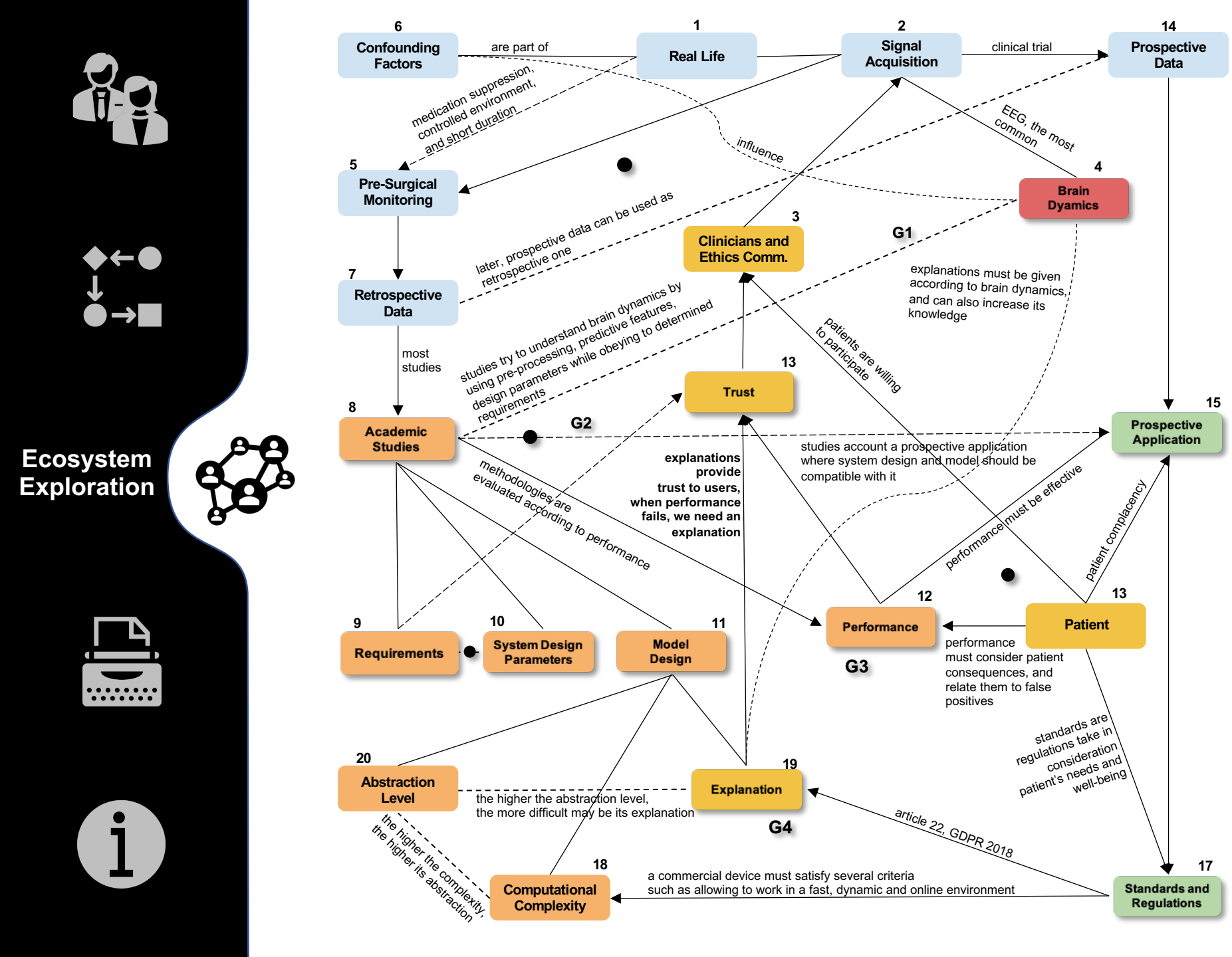
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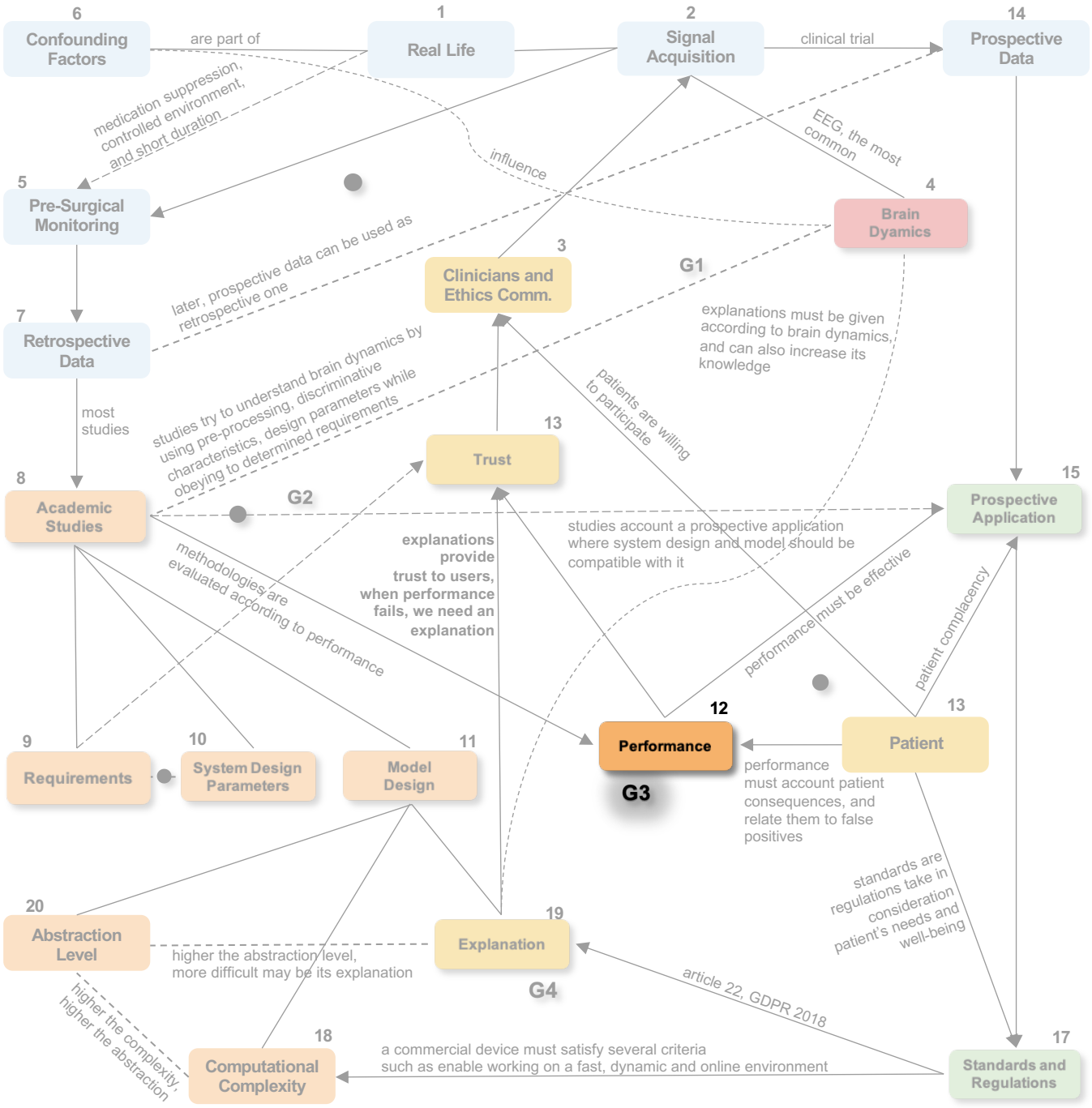
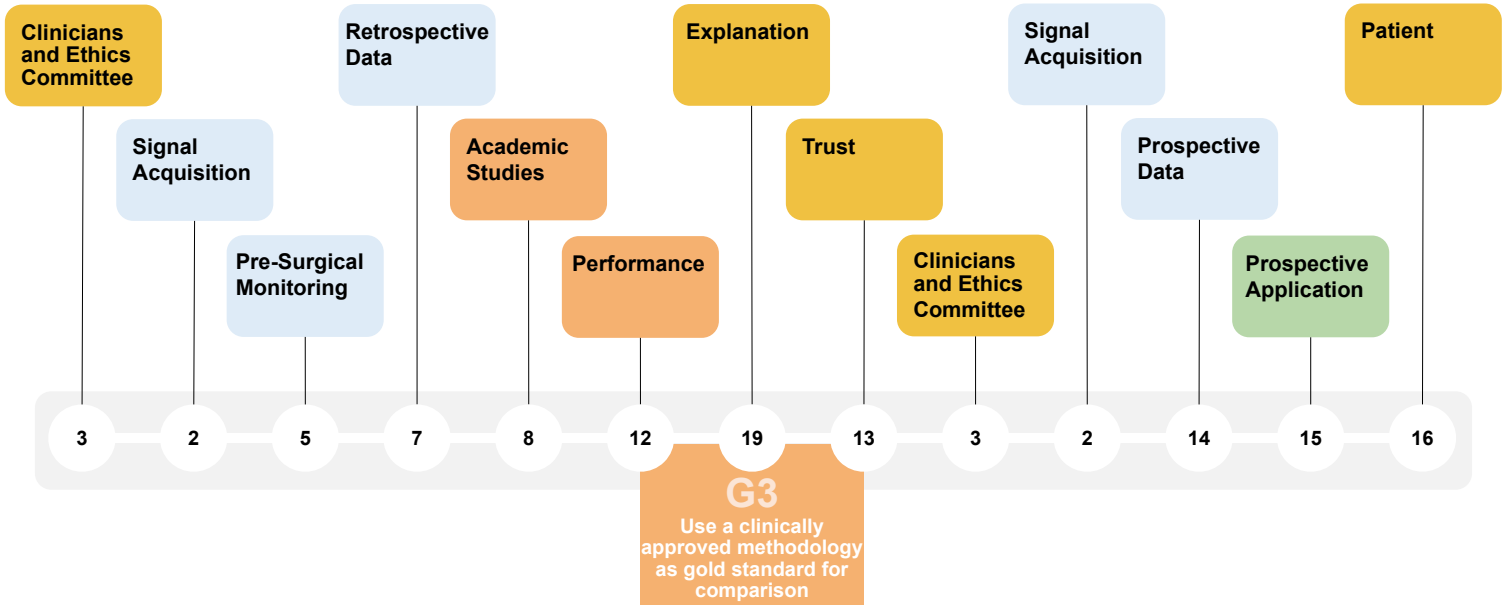


# Guideline 3

G3 is related to the use of methodologies that haven been clinically approved as a gold-standard for comparison. Reporting only sensitivity, specificity, and prediction above chance-level might be limited, as these metrics strongly depend on data and may not explicitly show progress. Thus, authors should compare their approaches with the ones already clinically approved. This comparison should not only be based on performance but also in explainability.

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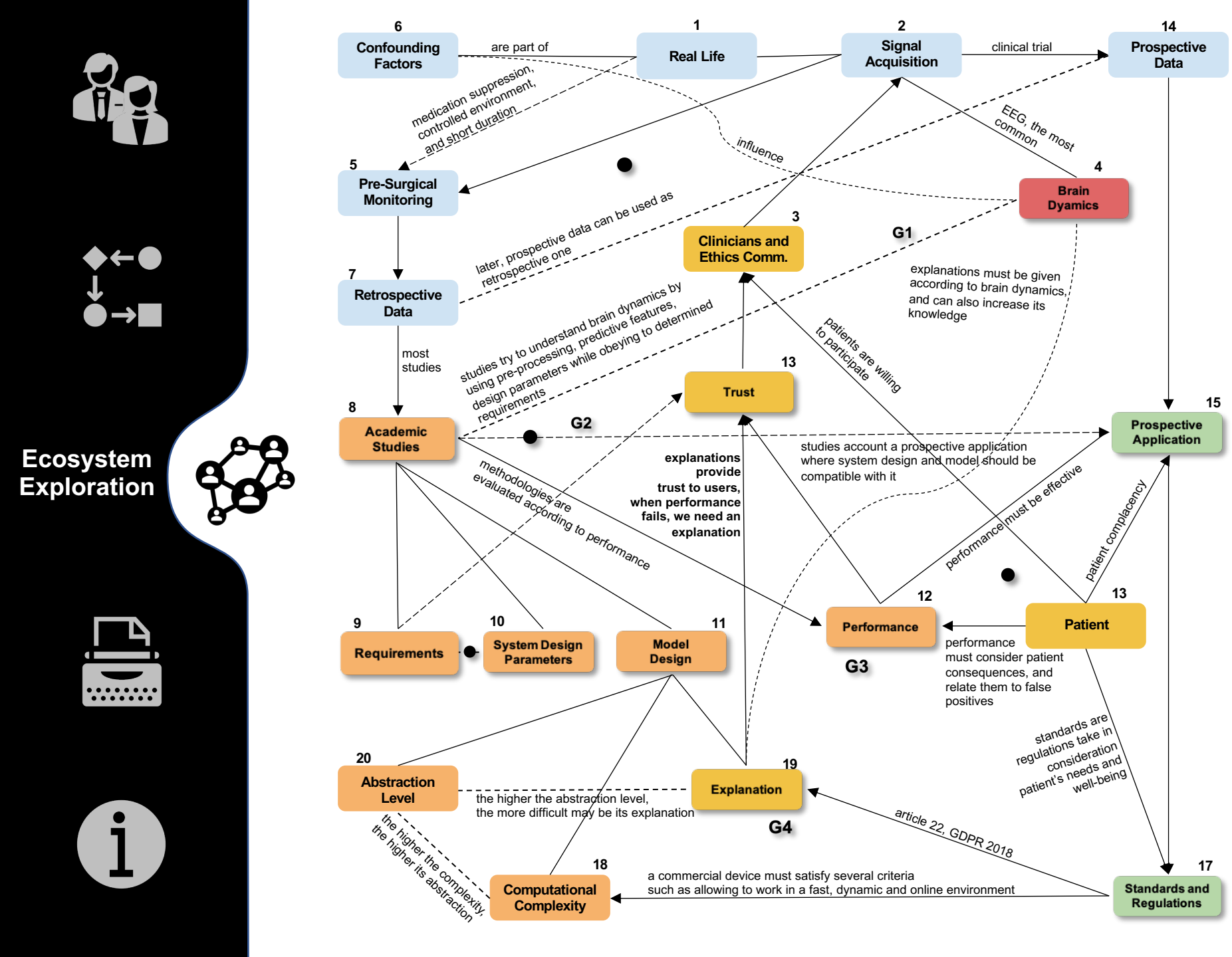
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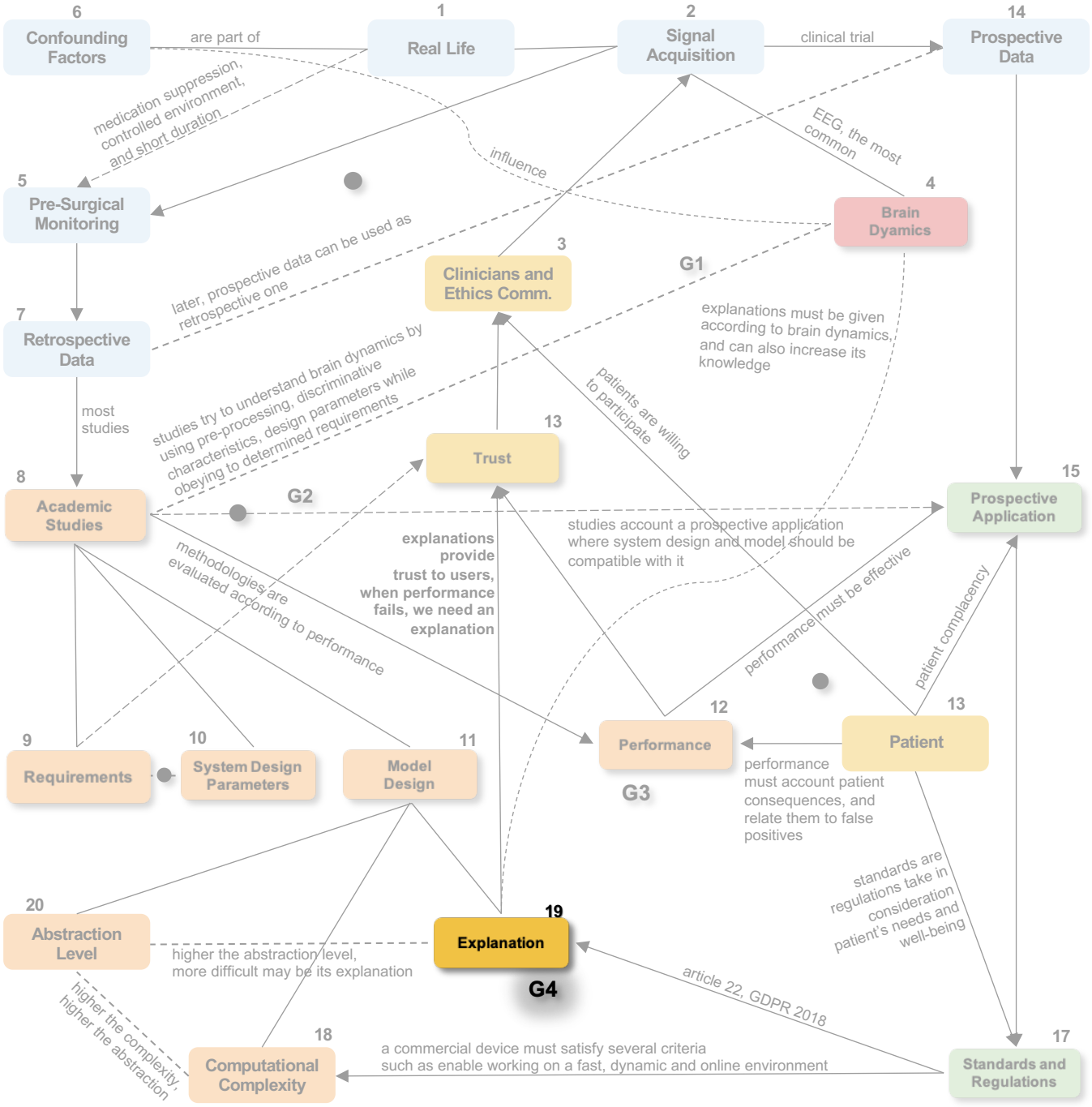
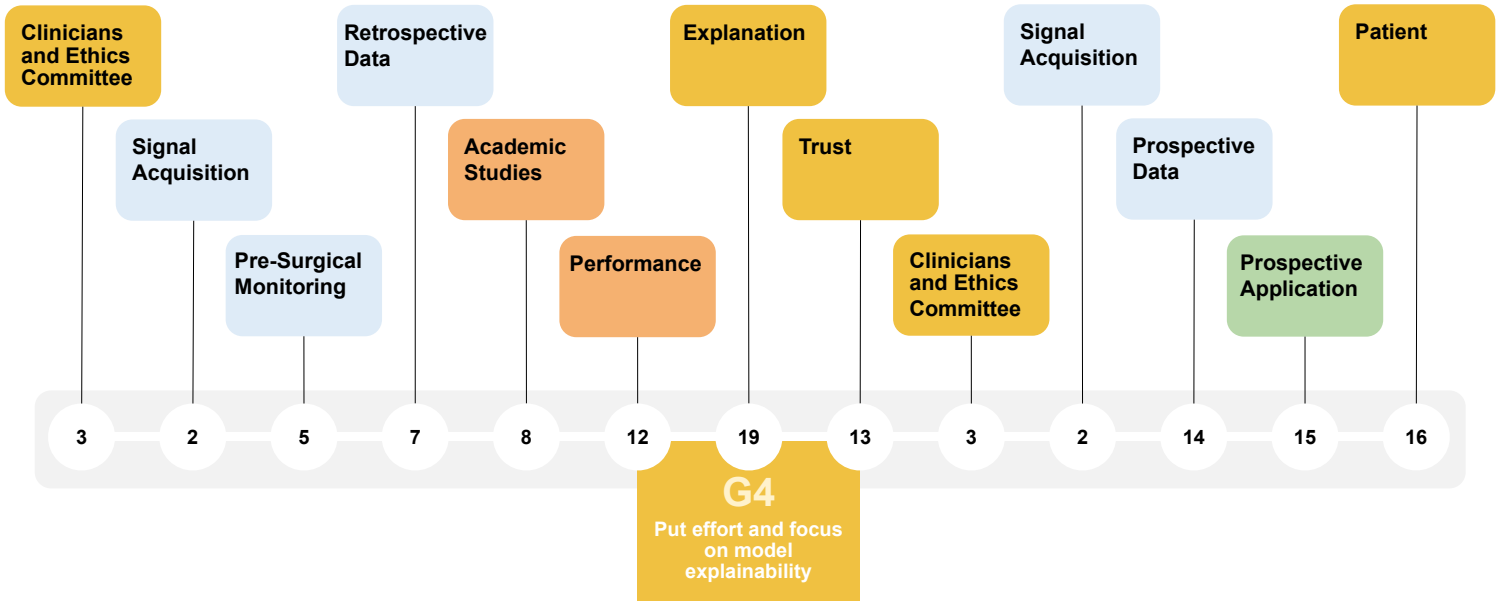


# Guideline 4

G4 is our most important guideline: researchers should focus on explainability (19) to promote trust among experts. It would be interesting to, at least, present a concrete example of model decisions throughout time. This way, it would demonstrate how a model could explain its predictions to an expert as a data scientist/clinician (application level), and a patient (human-level).

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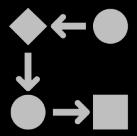

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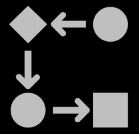


Discussion

# Discussion

## Limitations of the ecosystem

Despite being useful for clinicians and patients to understand this ecosystem, this study is directed to researchers that develop prediction approaches, so that they have a higher chance of clinical acceptance. Providing a comprehensible overview of all the ecosystem was difficult due to our data science/clinical background. Hence the natural bias/emphasis on academic studies.

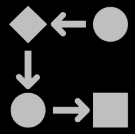
We analysed literature regarding seizure prediction that has been published over the last 46 years. In the future, we plan to undergo interviews to provide possible paths and sub-guidelines from the obtained. In the "Questions about the seizure prediction future" section in Supplementary Material, we present a series of questions that arose from describing this ecosystem which we would like to tackle and that deserve our attention.

Our greatest limitation was the patient role, as we did not properly include his/her agency. We strongly believe that we (the academic community) are still far from understanding what is it like to be a patient: the patients' expectations are largely different than the ones from clinicians and data scientists. In the future, we need to be more aware of the active role that a patient can have. The case of Dana Lewis and Hugo Campos are clear examples, where the patients might be able to track their data, analyze it and therefore, better control their closed-loop systems.

Dana Lewis created the “Do-It-Yourself Pancreas System” (#DIYPS), founded the open-source artificial pancreas system movement (#OpenAPS), and advocates patient-centred, -driven, and -designed research. She created #DIYPS to make her continuous glucose monitor (CGM) alarms louder, and developed predictive algorithms to timely forecast necessary actions in the future (https://diyps.org/about/dana-lewis/). Hugo Campos was diagnosed with hypertrophic cardiomyopathy: a disease in which the heart muscle becomes abnormally thick and that can be fatal. He received an implantable defibrillator, which is a device that electrostimulates the heart in case of dangerous arrhythmias. Simply put, after losing his health insurance, he bought a pacemaker programmer on eBay and learned how to use it with a two-week course. Hugo Campos is now a data liberation advocate and leader in the e-patient movement (https://medicinex.stanford.edu/citizen-campos/).

In fact, article 22 of GDPR 2018 not only provides patients with the right to have an explanation for any algorithm decision but also gives them the right to question those decisions. Despite oriented to seizure prediction, obtained guidelines and relations may be easily translated to different healthcare problems. Other conditions may benefit from a real-life intervention, such as the case of deep brain stimulation in Parkison's disease. Computer-aided diagnosis/prognosis software tools face similar problems on ethics, explainability, and trust given the high risk associated with model decisions in healthcare.

Next



Discussion

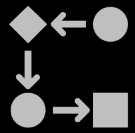
# Discussion
## Guidelines

About guidelines, G1 allows improving methodology comparison while delivering a deeper understanding of study limitations to clinicians (regarding assumptions on the underlying physiological mechanisms). For instance, it is interesting to note that, despite most authors with retrospective data use the pre-ictal concept as a point of no return, the two clinically approved studies deal use seizure susceptibility instead. G2 increases author comprehension on the limitations of signal acquisition methods and patient consequences associated with the obtained specificity.

Furthermore, increases in model performance at the cost of developing systems with unreal parameters may be questionable. Although large seizure occurrence windows may translate in higher performance, the interval to accept true alarms is larger. For the case of a warning system, we need to consider the levels of stress and anxiety-induced on patients or the consequences of frequent intake of rescue medication. We also need to understand how/if closed-loops intervention systems can be used with significantly long occurrence periods. We believe that, by considering an increase in performance as one of the primary goals of research, authors develop methodologies that may lack practical application. Although some studies may have a primary goal to increase knowledge on brain dynamics, researchers should clearly state limitations towards real application. Based on this, we encourage authors to study the consequences for the patients stemming from the development of a given seizure intervention system, through the definition of a maximum number of false alarms.

Concerning legislation and industry standards, we understand these as keepers of best practices on patient safety and trust among all actors. Holistic understanding of trust, explainability, and performance when developing a seizure prediction methodology may be the crucial aspect of this ecosystem.

These guidelines and used methodology can be applied to other healthcare settings using computer-assisted diagnosis/prognosis. However, we are aware that guideline G4 may differ among situation.



Discussion

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## The importance of explainability

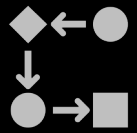
In 2007, Mormann et al. declared that algorithms were still too limited in performance to justify enrolling in clinical trials using responsive stimulation. Despite this paper is one of the most influential in seizure prediction, the first clinical trial (a warning system) started only three years later, in March 2010 and was published in 2013. The first clinical trial using responsive stimulation (phase III RNS System Pivotal Study, NCT00264810) started in 2005, which also led to the phase IV clinical trial (RNS System LTT study, NCT00572195) that started in 2006. Additionally, all current-generation of clinically approved studies and intervention devices use the detection of features alone, which demonstrates the importance of explainability.

Other examples are present in the literature that arose during discussion, as in 2014, Teixeira et al. tested the Brainatic, which is a real-time scalp EEG-based seizure prediction system, approved by the Clinical Ethical Committee at the Centro Hospitalar e Universitário de Coimbra. It computed 22 univariate features per electrode, and it used non-interpretable models, such as support vector machines, multilayer perceptron and radial basis functions neural networks. Based on this, we concluded that an increased performance cannot be the single criteria for a positive ethics committee decision. This shows that there is room for improvement, possibly by exploring more complex but still explainable systems. For instance, the RNS system might benefit from a more robust approach to capture dynamics before a point of no return. Towards this, more studies need to be performed to assess the algorithm effectiveness of responsive neurostimulation. Conclusively, as these methods have been clinically accepted and since a gold-standard comparison method is missing, they should be used as such, both for performance comparison and decision explanation.

Computational power has increased in the past years, which allowed deep learning approaches in several areas. Seizure prediction is no exception. As these approaches, along with rigorous preprocessing have a higher potential to handle brain dynamics, and as intrinsically interpretable models may not be a requirement to undergo a clinical trial, we believe there is an urgent demand for developing explainability methods that work on top of black-box models. There might be a tendency to argue that by requiring an explanation, the model will be limited in terms of performance.

However, we strongly believe that explanations may enhance the model's functioning, by tackling the incompleteness of problem formalization. In medical contexts, for example, a correct decision only solves our problem partially. We want to simultaneously deepen brain dynamics understanding, detect data bias, and improve model robustness. It is therefore important to understand possible trade-offs between potentially related aspects, that might not be easily recognized. All of these, when considered in an explanation, improve our understanding, which represents a way to promote patient safety and increases the chance of social acceptance concerning machine learning use.

Previous Next



Discussion

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## The specific case of seizure prediction

When predicting hospital mortality after acute coronary events, for example, there are established score models and therefore, using intrinsically interpretable models might be required to better integrate existing clinical knowledge.

In the case of seizure prediction, obtaining interpretability can become even harder because i) there is no clinical annotation on the pre-ictal period and ii) the EEG is still far from being fully understood. Therefore, it might be hard to replicate a methodology as there is no standardized protocol to manually identify the pre-ictal period.

When discussing case studies with clinicians on the EEG signal, we have observed that they often tend to point to/annotate spikes-and-wave discharges, activity increase, and rapid changes in the signal morphology and associate these to seizure events or seizure susceptibility. We suggest that a possible way "to engage in the clinical discussion", would be by using complex models such as Convolutional Neural Networks to capture complex dynamics, and then by delivering (pointing) to the EEG detected events that were considered for a given decision.

This type of explanation could be performed by using, for example, Local Interpretable Model Agnostic Explanations, and should be, beforehand, evaluated at the application level of explainability, by discussing these detected events with clinicians. This way, we might try to emulate the process of analysis of the EEG of an epileptic patient typically conducted by a clinician. Additionally, the use of such models may also unravel new patterns (EEG morphologies) that have not yet been associated with epileptic manifestations..

Indeed, we can see our body as a black-box system. In the case of antidepressants, for example, there is still no explanation for the delayed effect of antidepressant drugs and what neurochemical changes reverse the many different symptoms of depression and anxiety.

Simply put, we know the inputs (medication) and the outputs (the change in the patients) but we do not fully understand the underlying mechanisms. Nevertheless, these drugs are widely used because they are effective and their risk-benefit balance is favourable. Thus, we believe that the application of Machine Learning and the consequent requirements on interpretability/explainability will depend on the context and the available medical knowledge. For the specific case of seizure prediction, we argue the clinical use of deep learning approaches, as long as researchers put efforts in ensuring patient safety in each stage of each study and clinical trials. As long as researchers can ensure a good risk-benefit balance for the patient (for instance, by providing human-comprehensible explanations) and patients are willing to volunteer, it may even be unethical to forbid the use of these new methodologies.

As future work, we pretend to tackle the most relevant questions that arose during the previous stage by undergoing interviews with clinicians, data scientists, lawyers, and patients.

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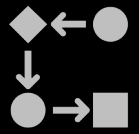
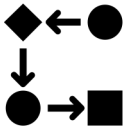


Information



## Product Process

When visualizing the product process, you can click “next” or “previous”, or in any step from the progress bar which represents a simplified version of this process. In any part, the product might suffer many iterations, as it is developed for a healthcare setting. Thus, ensuring patient safety is a priority.

## Ecosystem Exploration

When exploring the ecosystem, you can click on G buttons, on black circles, and boxes (that have shadow effects) to obtain more details. Actors are grouped into colours: signal acquisition and real-life (blue), studies (orange), people and exchanging beliefs (yellow), real-life application (green), and brain dynamics and disease heterogeneity (red). There are three types of relations: y is part of x (x-y); x occurs before y or x has direct influence in y (x→y); or x envisions y as a long-term goal or x indirectly influences y (x- -y).

## How to cite this paper

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