Challenges in the Use and Approval of Novel Diagnostic Agents

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This course will specifically discuss the challenges in performing clinical trials with novel diagnostic agents with high clinical potential. General guidelines will be given, and skills of the primary investigator required for good outcome will be discussed. More in detail, problems which may arise will be illustrated, using examples of new diagnostic MR agents. In this respect endorectal coil dynamic MRI & MRSI in prostate cancer, USPIO for detection of very small lymph node metastases, and a new oral MN-based liver contrast agent for improved detection of small metastases will be shown.

Once a promising novel diagnostic agent is developed, its safety and clinical efficacy needs to be tested. Only if a new agent is safe and effective, then there will be no problems with approval. Such an agent needs to provide improved information, preferably in a less invasive way, with improved therapy outcome, The clinical radiologist with affinity in performing trials is the key person in this process. In this course the skills needed and challenges facing this radiologist will be presented and discussed.

It is very important that a novel agent has the potential to bring something new to patient and health care. This usually is investigated and decided by the company producing the agent: *"go non-go decision"*. But equally important is the vision of the clinical radiologist who will be the "pusher" behind the clinical trial, whether the agent really is valuable. Examples shown will be the potential of a cellular -macrophages- contrast (USPIO) MR contrast agent in detecting minimal -3 mm- metastases in lymph nodes, blood pool contrast agents for MRA, and finally of an oral liver contrast agent for the improved detection of small liver metastases just by drinking a Manganese solution. It is crucial to continuously keep the clinical usefulness in mind when setting up, performing, and finalizing the results of a clinical trial with a novel agent. The endpoint(s), need to be carefully chosen based on the clinical potential of the agent and realizable. The study design must yield results, which allow to reach the endpoints. In this respect the most important issue is the "power analysis" which is needed to calculate the number of patients needed to prove the expected benefit of the new diagnostic technique compared to the old one.

The skills of the primary investigator, which are essential to the success of the trial are the ***"five P's"***: "Parties", "Persons", "Patience", "Persistence", and "Problem Solving".
In clinical trials there are many ***Parties***: the company who provides the agent, the center of the primary investigator, the other participating centers, the IRB, the patient organizations, and finally, the approving authority (FDA). To all of these parties the potential of the agent should be clear, and the way which will finally lead to the general use for the benefit of the patient must be discussed and assessed together, *before* the trial starts. As many different ***Persons*** are involved, the clinical radiologist performing the study should be a skilled communicator. Often the path from the initial recognition of its clinical potential to general use is a very long one –e.g. with the USPIO lymph node contrast agent this path is >15 years- thus from the involved radiologist it takes a lot of ***Patience***. Sometimes the hurdles to take are very high, nonetheless, if the potential clinical potential of a novel agent is very high, it is worth in putting a lot of effort in the trial. It thus requires a lot of ***Persistence*** of the primary investigator. Finally, one of the most important skill is the ability to find a solution, even in seemingly impossible situations: the **Problem Solving** capacity.

More specific challenges which arise in Clinical trials with novel diagnostic agents which will be discussed are: the use of different MRI systems, the related specific pulse sequence protocols, the performance and interpretation of the new technique, quality control, and safety aspects.