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LETTERS TO THE EDITOR

Communication near the end of life

To the Editor: We have read with interest the paper by Martoni *et al.*[1], which analyzed the use of chemotherapy in advanced cancer patients with a short life expectancy in Bologna, capital of the Emilia-Romagna region in northern Italy, between January 2003 and September 2005. The authors showed that 22.7% of patients of a series of 793 cases had received chemotherapy in the last 30 days of their lives.

We reviewed the medical charts of cancer patients with a short life expectancy followed by the Associazione Nazionale Tumori (ANT) Italia Foundation in the Lecce area, southern Italy, between September 2005 and December 2007, and found that 32.4% of patients of a series of 188 cases had received chemotherapy in the last month of their lives. We therefore confirm the inappropriate use of chemotherapy in the palliative care setting as reported by Martoni *et al.*[1] Overtreatment with chemotherapy in terminally ill cancer patients may have important negative consequences both for patients, with substantial worsening of quality of life, and the health-care system, with the risk of wasting resources[2].

One of the main reasons for this improper use of chemotherapy at the end of life is the patient's request, and many factors concerning the information/communication process may play a role. Quality end-of-life care is an ethical priority, and improving conversations about the end of life is an important part of improving that care[3]. Physicians are making progress in talking to their patients about the end of life, but a review of the literature on end-of-life conversations suggested that no physician can successfully undertake all aspects of this challenge[4]. The creation of a new professional role specialized in this area could be considered. This specialist would engage in a series of conversations to help the patient with advanced cancer receive the correct information, support his decision-making, and help him approach death in accord with his values and wishes[4].

Martoni *et al.*[1] concluded that, "The study suggests the urgent need to lay down guidelines for the appropriate use of chemotherapy in advanced cancer patients with a short life expectancy." However, clinical practice recommendations, mainly based on tumor response to last chemotherapeutic treatment and patient's performance status, are available to support physicians in avoiding overtreatment in the most common cancer types[5]. But the patient's request may often go against this endeavor. In our opinion, the key to solving the problem lies in ongoing conversations towards the end of life through the support of professional figures specialized in this area. This would actually contribute to limiting the inappropriate use of chemotherapy in the palliative care setting.

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IN REPLY

De Padova *et al.* identify the patient's request as one of the main reasons for the improper use of chemotherapy at the end of life and propose improving conversations with the terminally ill by means of the support of professional figures specialized in this area as a key solution.

We agree with De Padova in considering factors related to the information/communication process as being

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of critical importance to the appropriate assistance to these patients. However, other factors concur in creating the conditions for prescribing, or continuing to prescribe, anticancer treatments improperly to patients with a short life expectancy, namely, the suboptimal prognostication capability of oncologists, the training of oncologists as superspecialists in antitumor drugs, and the lack of local palliative care networks that effectively integrate the hospital, home-care programs, hospices, the primary care doctor, and the volunteer nonprofit associations.

When we suggest the urgent need to lay down guidelines for the appropriate use of chemothepy in advanced cancer patients with a short life expectancy, we are obviously not referring to the evaluation of the expected tumor response or to the patient's performance status. We think that guidelines should stem from an accurate analysis of all the above-mentioned factors, as well as include the role of professional figures such as psychooncologists.

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Clinical guidelines in advanced cancer: why we cannot avoid an evidence-based model

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To the Editor: Last year the *Journal of Clinical Oncology* published two interesting papers about the meaning of clinical guidelines in the treatment of advanced or terminal cancer[1,2]. Likewise, several months ago Martoni *et al.* remarked on the habit of medical oncologists to treat cancer patients until the last part of their lives, often using expensive treatment regimens. In the retrospective review published in this journal, they found that 101 (22.7%) of 793 patients who died of advanced cancer had been treated in the last month of their lives, and 36.6% of them had received costly new-generation drugs[3]. These 3 reports focus on a controversial question that is increasingly influencing clinical practice. At least once in our lifetime, all of us have treated a patient against any rationale and achieved a miraculous outcome. Nevertheless, anecdotal experiences and hopeful expectations cannot overcome the results of clinical research, in particular when the use of novel drugs or novel schedules goes beyond the limits set by their validated indications. The reasons for this habit are various and have been extensively analyzed and discussed[3-5]. Despite the consensus that the prolongation of anticancer treatments until the end of life is an index of low quality of care[6], the tendency to treat cancer patients until their very last days is becoming more and more frequent, to the detriment of time spent to favor comprehensive care of patients and their families[3,7-9]. Such an attitude in clinical practice is not supported by oncologists and palliative care experts, who suggest a comprehensive approach that integrates primary anticancer treatments with supportive care throughout all phases of the disease[10-13]. However, the 2 surveys investigating the trend in the aggressiveness of cancer care in an Italian[3] and an American context[8] suggest that clinicians often do not comply with this recommendation. A few years ago, the *Journal of Clinical Oncology* published an intriguing correspondence about the question, "But doctor, what have I got to lose...?"[14]. This is the same as to debate about "why or why not" treating a patient without any evidence of efficacy, or to opine that clinical evidence and clinical guidelines may not be enough to support decision-making in advanced or terminal cancer. Three controversial aspects are to be discussed in this regard:

- Does chemotherapy (or primary treatments against cancer) really represent the last resort for patients with advanced or terminal cancer despite the lack of any evidence of efficacy, with clinicians hopefully trusting in improbable miracles?
- Can the last part of the life of cancer patients really be considered a sort of no-man's-land without any rule, where everyone can do whatever they think best without any care for the evidence of efficacy?
- Can clinicians favor unjustified expectations in patients and their relatives, proposing primary treatments until the end of life without any care for side effects, lack of financial resources, and delayed patient referral to palliative care services?

Neither medical oncology nor palliative care are grounded on these bases. Although the requests of the patients and the habit of clinical oncologists reported by Martoni[3] and Earle[8] seem to suggest the impending surrender of evidence-based medicine in the last phase of life of cancer patients, such an issue must be analyzed and solved with "evidence-based" tools.

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Two problems should be tackled by both clinicians and researchers:

- How can the limits of an evidence-based approach to terminal cancer be conciliated with the expectations of the patients and their relatives?
- How can the duty to give all patients comprehensive care be conciliated with the needs and expectations of the single patient in daily clinical practice?

The patient-physician relationship is the fundamental dimension where therapeutic options have to be discussed, but it cannot be considered the sole dimension where the appropriateness of a choice is pondered. Although a physician must always do what he thinks best for the patient, his decisions should be aimed at optimizing outcomes on the basis of clinical evidence, or the resources allotted to those outcomes. We agree with Weil[1] and Kalemkerian[2] that guidelines and literature evidence are often not enough to solve certain questions in clinical practice, but we also agree with the opinion of Martoni that new guidelines for the last phase of life are urgently needed. Looking for evidence in advanced or terminal cancer is probably better than treating despite the lack of any evidence, and we believe that an evidence-based model of approach should be developed to guide *all* clinical choices for *all* patients and not for *one* patient with a particular problem. As reported by Weil[1], unexpected results may sometimes be obtained when treating patients against any evidence, but such an accidental and happy event will occur in much less than 5% of cases, i.e., the alpha error of evidence-based medicine, or the *P* value that any researcher looks forward to. In other words, we must not forget that the counterpart of an unexpected success is a failure rate greater than 95%, with a quite negative impact on patients, their quality of life and that of their relatives, and a huge waste of financial resources. Although clinical guidelines and an evidence-based approach are often not enough to solve the problems of patients with advanced cancer[1,2,15,16], an evidence-based model to approach all patients cannot be avoided before, during and after the patient-physician relationship. Our duty is not to treat *one* patient, but *all* our patients, and to achieve the best outcomes for *all* of them, employing adequate resources to achieve the outcome identified as the standard and refraining from improbable attempts to obtain improbable responses. *All* of our patients have the right to be treated with the highest expectation of response, and the expectation of response must be evidence-based. Likewise, our outcomes must be "cost-effective" in order to avoid personalistic and non-evidence-based approaches and a waste of resources. Combining an evidence-based approach, cost-utility considerations, and comprehensive care of advanced cancer patients will represent the new frontier of clinical research and clinical practice. Because of the slight chances of success and the risk of wasting our limited resources to pursue improbable benefits, the present gap between literature data and clinical practice is not enough to justify a clinical approach outside an evidence-based model.

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Hepatic abscess and silent underlying colon cancer: an emerging association?

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To the Editor: We read with interest the paper by Giuliani *et al.*[1] where a case of silent colon carcinoma presenting as a liver abscess with *Escherichia coli* was reported. Until a couple of decades ago, *Escherichia coli* was the most commonly isolated microorganism from liver abscesses. More recently, other gram-negative microbial agents have gained importance as emerging primary pathogens, e.g., *Klebsiella pneumoniae*[2-3]. On the other hand, the association between silent colon cancer and liver abscesses with different gram-positive strains including streptococci and staphylococci has also been described in the literature. In particular, cases of colon cancer and intraabdominal abscesses with isolation of *Streptococcus sanguis*[4], *Streptococcus milleri*[5], *Streptococcus intermedius*[6], *Streptococcus bovis*[7], and *Streptococcus viridans*[8] have been reported. We recently observed a rare case of the association between a retroperitoneal abscess caused by *Streptococcus milleri* and a silent colon cancer localized to the transverse colon and splenic flexure[9], with acute low back pain and sciatica as the first presenting signs. Moreover, an extremely infrequent isolation of *Staphylococcus hemolyticus* from a liver abscess has been recently reported by our group in a patient with asymptomatic colon carcinoma[10]. Thus, we agree with Giuliani *et al.*[1] about the importance of being aware that colon cancer can be an underlying cause of pyogenic liver abscess. In particular, when streptococci or staphylococci are isolated from a liver abscess, the existence of a primary, possibly neoplastic source outside the abdomen deserves careful consideration[2-11].

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Intestinal permeability and toxicity of second-line therapeutic agents in ovarian cancer

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To the Editor: We have read with interest the article by Li *et al.*[1] in which the authors describe their use of intestinal permeability testing to demonstrate the protective effect of oral glutamine administration in breast carcinoma patients treated with the combination of cyclophosphamide, epirubicin and 5-fluorouracil in the neoadjuvant setting. Although no difference was observed in the frequency of clinical manifestations of gastrointestinal toxicity, the lactulose/mannitol ratio was significantly lower in patients receiving glutamine

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supplementation. Myelosuppression and gastrointestinal toxicity are the principal side effects associated with most cytotoxic agents. Bone marrow toxicity of chemotherapy may be easily assessed, and laboratory parameters (e.g., peripheral blood cell count) that allow administration of chemotherapy can be clearly defined. By contrast, the assessment of gastrointestinal toxicity of chemotherapy still relies almost exclusively on anamnestic data that are inherently imprecise. The report by Li *et al.* illustrates the utility of intestinal permeability testing in objective monitoring of gastrointestinal side effects of chemotherapy, including the assessment of effectiveness of interventions aimed at alleviating the toxicity. We would like to point out another potential use of intestinal permeability measurements, i.e., predicting the toxicity of chemotherapy.

As a part of a project aimed at evaluating the potential of laboratory monitoring of gastrointestinal toxicity of cytotoxic agents used in ovarian cancer, we have evaluated intestinal permeability in 8 patients aged 58 ± 18 years (range, 35-79) with ovarian cancer treated with second-line therapeutic agents and 6 healthy women aged 53 ± 5 years (range, 46-60). Four patients had primary epithelial ovarian carcinoma and 4 patients had ovarian metastases from other primary carcinomas: pseudomyxoma peritonei in 2 patients, colorectal carcinoma in 1 patient, and gallbladder carcinoma in 1 patient. The second-line regimens included 5-fluorouracil (200 mg/m^2/day continuous infusion) alone (1 patient), or in combination with cisplatin (30 mg/m^2 weekly; 1 patient); topotecan (1.2 mg/m^2 day 1-5 every 4 weeks; 1 patient); gemcitabine (1 g/m^2 day 8 and 15 every 4 weeks) and 5-fluorouracil (750 mg/m^2 continuous infusion days 1-5; 2 patients); gemcitabine (1 g/m^2 days 1 and 8) and cisplatin (40 mg/m^2 days 1 and 8 every 3 weeks, 2 patients); and irinotecan (180 mg/m^2 day 1), 5-fluorouracil (400 mg/m^2 bolus and 600 mg/m^2 22-hour infusion days 1 and 2) and leucovorin (400 mg/m^2 days 1 and 2 every 2 weeks; 1 patient). Intestinal permeability was studied by measuring urinary sucrose, lactulose, xylose and mannitol after oral challenge[2]. Briefly, after an overnight fast, a pretest urine sample was collected to detect any endogenous mannitol and the patients ingested 100 mL of a test solution containing 2 g of mannitol, 2 g of xylose, 10 g of lactulose, and 25 g of sucrose in water. The patients then continued fasting for 2 hours, and urine was collected for 5 hours. Lactulose, xylose, sucrose and mannitol were determined by capillary gas chromatography, and urinary excretion was expressed as percentage of the ingested dose of xylose as well as lactulose/mannitol and sucrose/mannitol ratios.

Of the 8 patients investigated, 4 experienced serious (grade 3 or higher) toxicity during the first 28 days of therapy (grade 3 neutropenia, intestinal obstruction, grade 3 dehydration and early death). The baseline lactulose/mannitol ratio was significantly higher in patients who experienced serious toxicity (mean ± standard deviation; 0.14 ± 0.15 *vs* 0.02 ± 0.01, Mann-Whitney U test, $P = 0.03$). Compared to controls (0.03 ± 0.02), the lactulose/mannitol ratio was significantly higher (Mann-Whitney U test, $P = 0.04$) in patients with serious toxicity, but virtually identical to controls in patients without serious toxicity. During the first cycle, 1-2 weeks (8 ± 3 days) after the start of therapy, an increase in lactulose/mannitol ratio was observed in 6 of 7 patients (in 1 patient no subsequent measurement was obtained because of rapid progression). Figure 1 shows the course of the lactulose/mannitol ratio in 6 patients in whom at least 2 measurements subsequent to baseline were obtained. The lactulose/mannitol ratio increased, in most cases moderately, during the first cycle in all these patients, and the lactulose/mannitol ratio during the first cycle was significantly increased compared to controls (0.06 ± 0.03 *vs* 0.03 ± 0.02). On the other hand, the percentage of xylose absorption (13 ± 9% *vs* 12 ± 6%) and the sucrose/mannitol ratio (0.03 ± 0.02 *vs* 0.03 ± 0.02) did not change during the first cycle and were virtually identical to those of controls (12 ± 6% and 0.02 ± 0.01, respectively). The subsequent course of laboratory parameters of intestinal permeability during therapy was characterized by fluctuations.

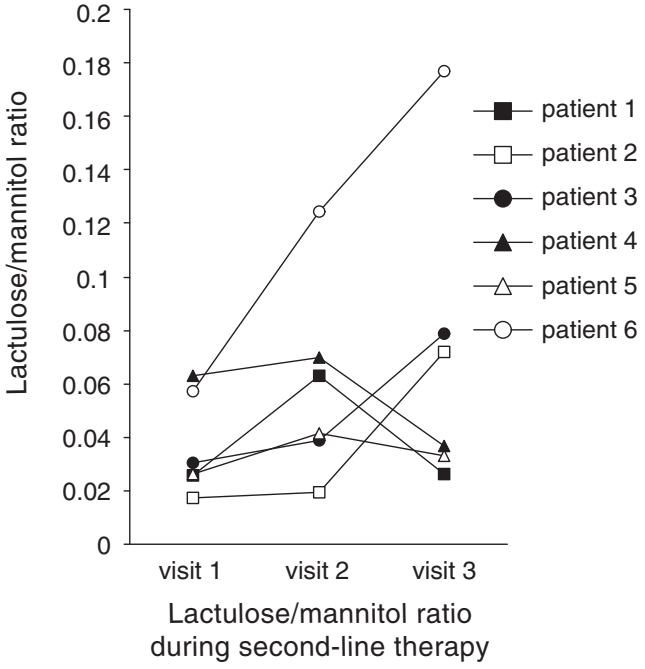

Figure 1 - Results of measurements obtained before the start of therapy (visit 1), during the first cycle, 8 ± 4 days after the start of therapy (visit 2), and at the end of the first or second cycle, 29 ± 18 days after the start of therapy in patients treated with gemcitabine (1 g/m^2 days 1 and 8) and cisplatin (40 mg/m^2 days 1 and 8 every 3 weeks; patients 1 and 4); gemcitabine (1 g/m^2 day 8 and 15 every 4 weeks) and 5-fluorouracil (750 mg/m^2 continuous infusion days 1-5; patients 2 and 5); topotecan (1.2 mg/m^2 days 1-5 every 4 weeks; patient 3); and 5-fluorouracil (200 mg/m^2/day continuous infusion) in combination with cisplatin (30 mg/m^2 weekly; patient 6).

The activity of second-line chemotherapeutic agents in ovarian cancer (topotecan, gemcitabine, etoposide, or fluoropyrimidines, alone or in combination with platinum) is compromised by considerable toxicity[3]. In many patients the limited benefit of administration of cytotoxic agents in patients with recurrent or refractory ovarian cancer may not justify the risk of sometimes life-threatening toxicity. In individual patients, the decision whether or not to start treatment with second-line chemotherapy could be difficult. Myelosuppression and gastrointestinal toxicity are the most frequent side effects common to most cytotoxic drugs, and these side effects are frequently associated. While myelotoxicity can be assessed easily by simple laboratory tests, the assessment of gastrointestinal side effects of chemotherapy still relies almost exclusively on anamnestic data. Monitoring, including the definition of parameters that allow safe administration of chemotherapy, is therefore difficult in the case of gastrointestinal toxicity. Measurement of intestinal permeability could be one of the approaches aimed at laboratory assessment of gastrointestinal toxicity of chemotherapy, including the prediction of side effects.

The term *intestinal permeability* was coined to characterize the barrier function of the bowel mucosa, and measurement of intestinal permeability was used for the study of benign disorders of small bowel mucosa. Intestinal permeability testing usually combines biologically inert sugars, a disaccharide and a monosaccharide. Under physiological conditions, monosaccharides are readily absorbed by the intestinal villi, while disaccharides that are absorbed in the crypt epithelium are excluded as villi limit the access of luminal contents to the crypts. Atrophy of the villi results in decreased monosaccharide absorption and increased exposure of the crypts to luminal contents. The resulting increase in the ratio of differential excretion of disaccharides and monosaccharides is an indicator of bowel dysfunction in inflammatory bowel disease and gluten enteropathy, but similar changes have been described in cancer patients treated with cytotoxic agents[4]. Laboratory parameters of intestinal permeability (e.g., the lactulose/mannitol ratio) are increased in cancer patients even before the start of therapy[5]. Although most studies of gastrointestinal permeability were focused on patients with gastrointestinal tumors[4,5], the present data indicate that changes of intestinal permeability may also be of importance in patients with gynecological tumors. However, different regimens incorporating 5-fluorouracil, gemcitabine and cisplatin were used in the patients included in the present study, and because of the limited size of the cohort the present results should be confirmed in prospective studies including larger series of patients treated with each regimen.

In conclusion, an increased pretherapeutic lactulose/mannitol ratio may identify patients who are likely to experience serious toxicity after administration of second-line cytotoxic agents used in the treatment of ovarian cancer. A moderate increase in the lactulose/mannitol ratio was observed during such therapy.

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Phase 0 trial as first human study in translational research in medical technology

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To the editor: Among the abstracts presented in the Translational Science Oral Session at the 2007 ASCO Annual Meeting, there was one reporting on the first phase 0 clinical trial designed to evaluate ABT-888, a poly (ADP-ribose) polymerase (PARP)[1].

The concept of the phase 0 trial was introduced in 2005 as a way for researchers to obtain pharmacokinetic and pharmacodynamic data earlier in the clinical drug development process. Phase 0 clinical trials are small first-in-man studies to determine a dose or a dose range which results in a desired biological effect[2,3].

For example, the ABT-888 trial reported that single-dose ABT-888 produced a greater than 95% inhibition of PARP in patients with a variety of solid tumors, opening the possibility of a phase I combination clinical trial with DNA damaging agents. So the target of the phase 0 trial was not the therapeutic intent or the dose scale toxic effects, but a demonstration of the effects of a single dose on physiological or pathological parameters, al-

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lowing expeditious development of future definite trials to get out the drug to general medical use[1].

Translational research is not only characteristic of pharmaceutical R&D, but of medical technology too. One of the most relevant problems in our technological research using new devices and/or diagnostic or therapeutic engines is the first application in humans after the mandatory step of preclinical studies. The passage to the clinical study is classic translational research. Generally, researchers invent and engineer a new prototype thanks to multidisciplinary support, then they apply the engine to animals, and lastly, before testing the potential application in phase I (maximal toxic energetic or temporal application), II (efficacy) and III (comparison with standard treatment) clinical trials, they need to verify if the diagnostic or biological effects of a determined technological application as observed in animals are the same in humans. This is similar to the problems related to a new surgical approach, where the feasibility and the biological impact of a new technique experimented in animals has first to be assessed in a non-surgical approach. In medical technological research, applications and results are usually verified faster than in pharmaceutical research, and introduction on the market follows after 3 to 5 years. This is the basis for the explosive growth of the medical scientific technology.

A more precise definition is needed for the scientific passage from the animal to the first clinical assessment, and this could be the concept of the phase 0 study. In medical technology research these first trials are generally referred to as pilot or feasibility studies, but their goals and terms may be ambiguous.

As an early-phase evaluation, the phase 0 clinical trial assesses the pharmacodynamics (how the body responds to a drug) or pharmacokinetics (how the drug behaves in the body) of a new drug to gather information about its potential effectiveness. A phase 0 study in medical technology will assess the first use of a technological innovation in humans, ascertaining whether its safety and biological effects are at least similar to those observed in animals. In this way, technological innovations that do not produce the desired effects can be abandoned and will not be moved onto phase I, II and III trials. Moreover, the timeline for new innovative developments can be shortened because phase 0 trials are performed in less time and with fewer patients than traditional trials[4-6]. Excalating maximal dose or energy dose delivering, therapeutic efficacy, and superiority over the clinical or diagnostic gold standard are the targets of the phase 0 translational trial.

Let us give some examples from our own experience. We built a new prototype using dynamic thermography for early detection of breast cancer as a diagnostic screening tool before mammography. As the first test in women we needed to verify in a few selected breast cancer patients with an established tumor size if the thermographic images corresponded to the results of preclinical studies. The sensitivity and specificity will be explored in subsequent trials. Another case is virtual gastroscopy. We are verifying if CAD 3-D reconstruction with established mathematic algorithms of multislice CT images of the human stomach gives the same promising definition as CT images in animals, enabling the future use of virtual gastroscopy for screening and/or clinical use like that of virtual colonoscopy. The assessment of the impact (sensitivity, specificity and patient compliance) of this new radiological tool in future daily routine will follow. Last but not least, we are planning to test hyperthermic focused ultrasound (HiFus) energy in murine liver and lung tumors. The coagulative necrosis effects of a defined timely and energetic ultrasound dose and its safety in humans will be verified in a phase 0 trial where we will evaluate by histological examination in a few patients if the hyperthermic necrosis and apoptosis observed in mice is confirmed in man. Possible future alternative or complementary indications of the HiFus procedure will be studied in phase I (maximum possible localized safe temperature delivered), phase II (efficacy of ablation in liver and lung cancer) and phase III (alternative to the standard surgical approach) trials.

In conclusion, phase 0 studies could improve the demonstration of the safety and biological effects of a particular diagnostic or therapeutic technological innovation in humans, allowing expeditious development of future trials to make it ready for general medical use. The definition of the parameters (assessed in animals) and goals (equivalent safety and biological effects) of a phase 0 trial in medical technology can standardize the still undefined pilot or feasibility studies in man.

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