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PERSPECTIVE

Feasibility and challenges of independent research on drugs: the Italian Medicines Agency (AIFA) experience

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KEY POINTS

- National Health Service (NHS) is becoming increasingly aware of the need to support independent research to answer some important questions for patient care in areas of scant commercial interest.
- This article reports the main features and strategies of the independent research programme on drugs launched by the Italian Medicines Agency (AIFA) in 2005.
- In the three bids launched between 2005 and 2007, a total of 151 studies have been approved for funding for a total of about 78 million Euro.
- In this article we describe the Italian legislative framework under which the programme was launched, the types of research funded and discuss how the supported studies could contribute, in an international framework, to the knowledge needed on drug efficacy, effectiveness and safety.

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The need for independent research

Much of the investment in biomedical research is directed towards basic research. In the UK and USA, for instance, over two-thirds of current investment is in basic research, with the remaining 30% for applied research [1,2]. Less than 10% is invested in comparisons of interventions and less than 1% for health services research. Practice-oriented clinical research is mainly supported by pharmaceutical companies [3]. However, many clinical research questions are considered too risky, or not economic, for drug companies and remain unaddressed. Thus, there are not enough studies with robust end-points and long-term follow-up that can really tell us what is the added value and appropriate therapeutic role of drugs [4,5]. In addition, under-represented populations such as children, pregnant women and the very elderly are frequently excluded from company-sponsored trials, so they end up being treated with drugs used off-label [5].

Over the past 20 years, the efficiency of the drug innovation and discovery process has fallen. There are fewer new approved drugs [6] and they provide only a limited advantage over previously available options [7], usually at higher cost [8]. With evidence for only half of health-care decisions, there is a substantial need for additional studies to support evidence-based practice [9]. National Governments have, however, to build a formal and sustainable funding scheme for clinical comparative research in the areas less explored by company-sponsored trials.

In 2005, the Italian Medicines Agency (AIFA) started an innovative programme to promote independent clinical research on drugs under a mandate that widens the traditional activities of a regulatory agency, including a strong commitment to independent information and evaluation of drugs prescription patterns [10,11]. This article describes the AIFA's programme, with specific emphasis on the funding mechanism, research areas and the characteristics of funded studies over the past three calls for proposals (2005–2007). We also discuss whether these studies are in fact contributing to overall knowledge of comparative drug efficacy and safety questions.

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AIFA'S role in independent research

AIFA is a regulatory institution operating within the Italian Ministry of Health (http://www.agenziafarmaco.it). Its activities include marketing authorization of medicinal products, pharmacovigilance, inspection of products and manufacturing processes, monitoring ethics committees and maintaining the Italian Clinical Trial Register (http://oss-sper-clin.agenziafarmaco.it/index_ingl.htm). Promotion and direct funding of relevant independent research on drugs is a strategic task of AIFA.

Non-profit research was first regulated by law in 2004 [10]. The legislation supports investigators in public and non-profit institutions. It describes the main characteristics studies must have to be eligible for funding under this scheme: (i) researchers must have complete control of the study design and conduct (i.e. protocol, data analysis, reporting results) and not involved in patent ownership; (ii) full publication of results is mandatory; and (iii) the study should not be part of the drug registration process.

Finance for this programme comes through an innovative policy: all international and national pharmaceutical companies operating in Italy are required to contribute 5% of their yearly expenditure for promotional initiatives targeting Italian health professionals to a national fund for independent research [11]. Promotional activities include advertisements, supporting material – visuals, software, books, etc. – seminars, congresses, trade fairs, freebies and gifts, but salaries of drug representatives or marketing employees are not considered. In the first 3 years of the programme, around 45 million Euro per year have been made available: 50% of funding supports independent research and independent drug information [12,13] and 50% the reimbursement for orphan and 'life-saving' drugs not yet marketed.

Areas of interest of the AIFA'S research programme

In the 2005–2007 call for proposals, three main areas of drug research were included:

- *Orphan drugs for rare diseases and drugs for non-responders*, dedicated to trials of orphan drugs (approved or 'designated' by the EMEA), drugs used off-label for rare diseases and benefit/risk evaluation of therapies for non-responders to standard treatments. Studies were expected to adopt a comparative design.
- *Comparative studies (including head-to-head comparison of drugs and therapeutic strategies)*, dedicated to phase III-IV RCTs comparing the benefit-risk profile of treatments; at least one of the drugs investigated needed to be reimbursable by the Italian NHS.
- *Appropriateness of drug use, pharmacovigilance and outcome research*: this concerns marketed drug whose benefit-risk profile needed to be better defined. Design can be either experimental or observational. Quality improvement studies to boost the appropriateness of drug prescription and RCTs with non-pharmaceutical comparators were included as well as studies testing the impact of educational interventions on appropriateness of drug utilization. From the 2007 call, systematic reviews (SRs) have been included as specific research topic in the third area and the call explicitly asked for SRs able to identify knowledge gaps so that specific research priorities could be included in subsequent AIFA's calls for proposals.

The Annual Call

A Research and Development Committee (R&DC) oversees the programme, providing strategic guidance, identifying research topics of interest and eligible protocol conditions such as selection of clinically relevant end-points, long-term follow-up, inclusion of patient populations normally under-represented (e.g. children) in RCTs conducted for registration purposes. The R&DC solicits information on AIFA and NHS priorities and consults through ad hoc face-to-face meetings representatives of Italian medical, scientific and governmental institutions, the Italian Federation of Pharmaceutical Companies, medical faculties and regional health authorities. The consultation process included also an online freely accessible dedicated section of AIFA's website, which allows researchers, health professionals and the general public to suggest topics before the call is finalized. The evaluation procedures mirror the standards of internationally recognized funding bodies, such as the US National Institutes of Health. The criteria for project assessment are: (i) relevance to clinical practice within the NHS and AIFA regulatory activity; (ii) scientific validity and (iii) background of the principal investigator and organizational experience. Applicants are asked to specify the expected added value of their project to the overall available evidence, to avoid futile duplication; they also have to disclose any potential competing interests. International clinical trial registers, such as ClinicalTrials.gov are then searched to check the potential overlaps with RCTs that are already ongoing or planned. Investigators first submit a letter of intent and those deemed most important by the R&DC undergo thorough peer review by national and international referees, different from those serving in the R&DC, whose identity is not made known to the applicants. Study protocols are ranked on the basis of the referees' scores within each topic of the three areas of the call and, starting with the highest score, funds are distributed

accordingly. The results of the evaluation process are made public.

Proposals received and funded in 2005–2007

Of a total of 1217 letters of intent submitted in response to the first three calls, 151 studies (12%) were approved for funding for a total of about 78 million Euro (Table 1). Institutions from all the Italian regions are involved in different projects (Fig. 1). Out of the 151 funded projects, 115 (76%) focus on patient populations such as children (36 studies), pregnant women (6 studies) and the elderly (73 studies mixing adults and elderly); 25 studies are exclusively dedicated to the paediatric population and three exclusively to the elderly. The largest share of funded studies (64, 42% of total) was in the area of orphan drugs for rare diseases. In a considerable proportion (18 studies; 26%), the focus was on ultra-rare diseases, i.e. with a prevalence lower than 1 per 100 000 inhabitants.

Most funded projects were experimental clinical studies (114; 75%), followed by observational studies (19; 13%), education interventions (13; 9%) and systematic reviews (5; 3%), the last included since 2007. Within the experimental studies, a majority (92; 81%) had a comparison group; non-controlled studies (22; 19%) were only funded for rare diseases. Oncology and neurology are the most frequent therapeutic areas (Table 2). The area of rare diseases mostly comprises a number of projects under the headings of genetic diseases and immunology.

To illustrate the types of projects funded under this programme, Table 3 gives a short description of the background and clinical relevance of some trials. Briefly, the examples aim to highlight the key objectives of AIFA's bid, i.e. contributing to the scientific assessment of the benefit-risk profile of drugs in areas where methodologically sound studies are scant, important uncertainty remains and therefore regulatory decisions need to be informed by better evidence.

The two breast cancer studies aim to assess whether a treatment shorter than the one approved is equally effective and has lower toxicity (i.e. Short-HER study) and a head-to-head comparison of the benefit-risk profile of the three marketed aromatase inhibitors (i.e. FATA study). Moreover, the second breast cancer study, as well as that in multiple sclerosis, will directly compare the therapeutic value of generic drugs (tamoxifen and azathioprine respectively), a comparison which can hardly be expected to be done in company-sponsored research. The fourth example is a typical prevention trial which will provide new knowledge – with high public health relevance for many other countries – on the best daily dose of folic acid supplementation for the reduction in congenital malformations. The fifth example is a study on HBV vaccination and should be viewed as a post-marketing study on the long-term efficacy of a hexavalent vaccine withdrawn from the international market because of a decreased immunogenicity of the hepatitis B component [14]. The Niemann Pick trial (sixth example) is expected to confirm or disprove preliminary evidence coming from the only industry sponsored trial while treating all the Italian population presenting the disease. This also allows the strictly controlled introduction of a drug on the market avoiding its extensive off-label use. The last example in Table 3 is a comparative trial on Juvenile Dermatomyositis (a rare disease), involving more than 180 centres worldwide, which demonstrates that it is possible to conduct a robust comparative trial on rare diseases and underlines the importance of international cooperative research networks.

AIFA's scheme was not simply an additional source of funding, but an opportunity for integration: researchers could apply for additional support of projects (partly) funded from a different public or non-profit institution. For instance, AIFA contributed to a study supported by Telethon, extending the number of patients receiving an innovative treatment for a rare, severe congenital immunodeficiency [15].

Table 1 Projects of the Italian programme for independent research on drugs, by research area

	Call for proposals 2005			Call for proposals 2006			Call for proposals 2007			Total			
	Letters of intent	Funded protocols		Letters of intent	Funded protocols		Letters of intent	Funded protocols		Letters of intent	Funded protocols		Budget
Area	*N*	*N*	%*	*N*	*N*	%*	*N*	*N*	%*	*N*	*N*	%*	× 10^3 €
1. Rare diseases	150	20	13	184	24	13	120	20	17	454	64	14	13·701
2. Comparative trials	80	13	16	121	16	13	101	9	9	302	38	13	39·107
3. Pharmacoepidemiology	172	21	12	149	11	7	140	17	12	461	49	11	25·350
Total	402	54	13	454	51	11	361	46	13	1·217	151	12	78·158

*Funded protocols as a percentage of the letters of intent.

Figure 1 Regional distribution of the 151 funded protocols and numbers of units participating in the project (in brackets). In three regions (white), no principal investigators have been funded, although several research units participate in other multicenter studies funded by the programme.

A full list of funded projects is available as Appendix 1. A detailed activity report, in Italian, is available from the authors on request.

Discussion

We have reported the experience of the first 3 years of AIFA's activities. Four years after launching the first call for proposals, at least three key features of AIFA's experience are worth emphasizing:

- First, the alignment that this research scheme achieved of regulation and knowledge production. AIFA is in fact an Agency that can, by mandate, fund the research that is needed to inform its regulatory decisions.
- Second, the wide consultation of stakeholders (researchers, payers, pharmaceutical companies and others) that precedes the finalization of the call, which provides extensive input about 'open' research questions that experts alone may be unable to identify systematically.
- Third, the attempt to involve pharmaceutical companies actively in the funding scheme through consultation and opportunities for collaboration in some studies.

Our experience also reveals that time is needed before real changes will occur. We learnt that making resources available for independent research is a necessary but not sufficient condition for assuring that research reflects patients' needs. The relevance and breadth of the proposals submitted (especially for comparative trials) varied considerably. Oncology and cardiovascular disease were the areas where the mostly scientifically sound and relevant proposals were received and funded. There were also 'orphan areas' – such as anaesthesiology or orthopaedics – in which there have been a dearth of acceptable proposals. This is presumably attributable to the more limited research experience of health professionals working in these

Table 2 Therapeutic fields of studies funded under the AIFA calls 2005–2007

	Research areas			
	1	2	3	Total
Therapeutic fields†	***N (%)***	***N (%)***	***N (%)***	***N (%)***
Oncology and haematology	19 (30)	10 (26)	3	32 (21)
Neurology	3 (5)	4 (11)	17 (35)	24 (16)
Genetic diseases	17 (27)	–	1 (2)	18 (12)
Immunology	10 (16)	2 (5)	3 (6)	15 (10)
Infectivology	2 (3)	2 (5)	9 (18)	13 (9)
Nephrology	3 (5)	6 (16)	1 (2)	10 (7)
Cardiology	2 (3)	1 (3)	5 (10)	8 (5)
Endocrinology	3 (5)	4 (11)	–	7 (5)
Respiratory diseases	–	4 (11)	2 (4)	6 (4)
Eye diseases	3 (5)	–	–	3 (2)
Pain therapy	–	2 (5)	1 (2)	3 (2)
Other*	2 (3)	3 (8)	7 (14)	12 (8)
Total	64 (100)	38 (100)	49 (100)	151 (100)

Values are given as *n* (%). Research areas: (1) Orphan drugs for rare diseases and drugs for non-responders; (2) Comparative studies, including head-to-head comparison of drugs and therapeutic strategies; (3) Appropriateness of drug use, pharmacovigilance and outcome research.
*Other: includes gastroenterology and hepatology, pregnancy, anaesthesiology, education interventions, etc.
†Diseases were classified following the International Classification of Diseases 10th edition (ICD-10).

fields. Medical specialties with limited traditions of research methods need mentoring and training within the NHS, if we want to export the value of research across medical fields. On the other hand, the persistence of 'orphan questions' in areas with otherwise solid research traditions might reflect investigators' reluctance to commit themselves to long-term projects perceived as not 'cutting edge' research. Independent research may also be seen as a potential threat to the relationship with pharmaceutical sponsors that fund the majority of trials. There is no easy solution to this latter issue and it presents cultural and ethical challenges for the NHS. It is reasonable to assume that in areas that are 'true high priority orphan areas' specific calls should be present in the bid for several years so that research groups willing to undertake the challenge would develop the necessary confidence and would eventually emerge.

As in many other countries, once scientifically sound trials have been funded, substantial time is still needed to initiate patient recruitment given the many administrative requirements that in non commercial research have a particularly negative impact due to the lack of an appropriate research infrastructure [16].

While Italy has had outstanding examples of independent pragmatic trials carried out by large cooperative groups in oncology and cardiology, substantial efforts are still required to establish research consortia that are able to recruit large numbers of participants, ensuring data quality, especially in other disease areas. The overall improvement in research capacity that the AIFA programme is generating therefore represents added-value for industry-sponsored trials as well. Moreover, companies (as well as medicines agencies) may use the findings of AIFA-funded trials to support information in regulatory procedures.

Our experience suggests that it would be important to look for a joint funding stream at European level [16]. Very few independent multinational studies are being funded and this is an important limitation, especially for patients with rare diseases. Sharing priorities and agreeing to fund pivotal cross-national studies are obvious directions that should be considered.

If the experience we have described continues, AIFA will have to develop an appropriate dissemination strategy to facilitate the uptake of its research results.

Table 3 Example of trials funded under the AIFA programme on independent research on drugs

	Field	Clinical question relevant for the NHS	The AIFA study	Why independent research is needed	Design	Estimated patients	Primary endpoint
1	Oncology (early breast cancer)	Optimum adjuvant treatment duration with trastuzumab (shorter treatment may give comparable efficacy with significantly lower toxicity and cost)	Effects of adjuvant chemotherapy plus 3 or 12 months of trastuzumab in breast cancer HER2-positive patients	No commercial interest	Non-inferiority RCT, open label, active controlled	2500 women	Disease-free survival
2	Oncology (early breast cancer)	Which aromatase inhibitor for adjuvant treatment of postmenopausal patients with endocrine-responsive breast cancer, and which strategy (upfront or sequential) is more effective and safe?	First Adjuvant Trial on All (FATA) aromatase inhibitors in early breast cancer to compare anastrozole, letrozole and exemestane, upfront (for 5 years) or sequentially (for 3 years after 2 years of tamoxifen)	Only an independent sponsor can be interested. No cutting-edge research question	Superiority RCT (adopting a 3 x 2 factorial design), open-label, active-controlled	3600 women	Disease-free survival
3	Neurology (multiple sclerosis)	In a systematic review azathioprine (a generic drug) was found as effective as interferon (INF) beta, at much lower cost	Comparison of the efficacy and safety of azathioprine and interferon-beta in patients with multiple sclerosis	Results may be unfavourable to the patented drug	Non-inferiority RCT	360 patients	Cumulative relapse count
4	Prevention of congenital malformations (CMs)	It is still not clear whether folic acid (FA) supplementation has a preventive effect on CMs beyond those of the neural tube. Another question concerns the dose–response relation of FA (0·4 mg vs. 4 mg)	Comparison of FA peri-conceptional supplementation of 4 mg/day with the 0·4 mg/day standard dose on reducing the occurrence of all CM	Orphan public health problem	Superiority RCT, double-blind, active controlled	5000 women	Reduction of all CMs
5	HBV vaccination in children	In 2005, the EMEA withdrew the marketing authorisation for Hexavac (a hexavalent vaccine) because of concerns about the long-term protection against hepatitis B virus (HBV). At the moment of market withdrawal around half of Italian neonates had been immunized with Hexavac in their first year.	To establish whether children vaccinated with Hexavac need a booster dose of HBV vaccine or a complete new course of vaccination to ensure long-term protection	No commercial interest	Observational cohort study	Two cohorts of 700 children	HBV immunological response

Table 3 *Continued*

	Field	Clinical question relevant for the NHS	The AIFA study	Why independent research is needed	Design	Estimated patients	Primary endpoint
6	Genetic disease	No treatment is approved for Niemann Pick disease type C (NPC). Only one trial (company-sponsored) is currently ongoing	Evaluation of the efficacy and safety of miglustat for all Italian patients with NPC	Lack of commercial interest as the drug (used off label) was already reimbursed by the NHS	Single-arm trial, open-label.	24 patients	Arrest of progression or improvement in neurological involvement and swallowing abnormalities
7	Rheumatology	Current treatment for juvenile dermatomyositis (JDM) has failed to eliminate significant morbidity and mortality and no comparative RCTs have ever been done in children	Evaluation of the best treatment for children with JDM	Limited commercial interest	Superiority RCT, single-blind, active-controlled	120 children	Time to clinical remission; time to flare of disease

Another important indicator of success of the independent research programme will be the demonstration that some funded studies influence AIFA regulatory decisions. This is consistent with the general reflection on how to stimulate the acquisition of data needed to improve evidence-based decision making [17,18].

Our experience should also be seen in a wider context. Investments in independent and comparative effectiveness research are increasingly seen as a strategic asset of national health systems. In early 2009, President Obama supported the American Recovery and Reinvestment Act, with a total investment of $1·1 billion to 'accelerate the development and dissemination of research assessing the comparative effectiveness of health care treatments and strategies' [19]. Other European countries (e.g. Spain) are also taking steps in this direction although there is a great variability in the models adopted with regard to structural, financial, technical and procedural principles adopted [20]. Common features are the strong endorsement by policymakers, independence and scientific rigour and increasing attention to costs [21]. All these national efforts should promote the identification of shared priorities and agreements to fund pivotal cross-national studies.
Further benefits would be the improvement in the quality of clinical research, the avoidance of duplication of effort, and the production of additional evidence to reassess new and old drugs and increase the appropriateness of clinical practice [22–25].

While this article gets published, the proposals selected for the 2008 AIFA's bid have gone through their full peer review and 38 have been funded by AIFA Management Board (Consiglio di Amministrazione) and awarded a total of 11·5 million Euro. The 2009 bid developed according to the same philosophy and approaches described in this paper is currently under evaluation by the Agency Board.

Box 1. Important messages

- In Italy, a funding scheme based on 5% promotional expenditures of pharmaceutical companies has been used to support an independent research programme on drugs, coordinated by the Italian Medicines Agency (AIFA).
- The AIFA programme has funded comparative trials, trials on rare diseases and studies aimed at improving the appropriateness of drug use.
- In the first 3 years of the programme, 151 studies have been funded and initial results are expected in 2010.
- A common international effort to fund independent research, as well as strengthening the research infrastructure, is urgently needed.

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Competing interests

All co-Authors of this paper are AIFA's members (though Research & Development Committee members are not AIFA's employees) and thus their judgments could have been influenced by their commitment to the implementation and success of the research programme.

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Appendix 1

Funded studies within the three calls for proposals launched (2005–2007)

a) list of the 64 projects funded within the Area 1 (orphan drugs for rare diseases) of the three AIFA calls for proposal (2005–2007).

No.	Principal Investigator	Call (Year)	Study title
1	Abbate Mauro	2007	A prospective, sequential study to assess the efficacy of rituximab therapy in maintaining remission of nephrotic syndrome after steroid and immunosuppressive therapy withdrawal in patients with steroid-dependant or multirelapsing minimal change disease or focal segmental glomerulosclerosis
2	Aiuti Alessandro	2005	Safety and efficacy study of gene therapy with autologous $CD34^+$ cells transfected with a retroviral vector encoding the adenosine deaminase (ADA) gene (EMEA/OD/053/05) for the treatment of severe combined immunodeficiency due to the lack of ADA
3	Andria Generoso	2005	Efficacy and safety of treatment with *N*-butyl-deoxynojirimycin (NB-DNJ-miglustat) in patients with Niemann-Pick disease type C
4	Andria Generoso	2005	Multicentre study of the efficacy and tolerability of tetrahydrobiopterin in a paediatric population affected by phenylketonuria
5	Ardizzoni Andrea	2006	Multicentre phase III randomized study of cisplatin and etoposide with or without bevacizumab as first-line treatment in extensive stage (ED) small cell lung cancer (SCLC)
6	Barbui Tiziano	2006	Intensity of cyto-reductive therapy to prevent cardiovascular events in patients with polycythemia vera (PV) – CYTO-PV
7	Bassan Renato	2006	A multicentre randomized trial in adult patients with acute myelogenous leukaemia (AML), to compare (i) a standard-dose versus high-dose remission induction regimen, and (ii) an autologous blood stem cell transplantation versus an autologous blood stem cell-supported multicycle high-dose chemotherapy programme, within a risk-oriented post-remission strategy reserving allogenic stem cell transplantation for high-risk cases
8	Beghi Ettore	2005	Double-blind placebo-controlled trial on the use of acetyl-L carnitine for the treatment of amyotrophic lateral sclerosis (ALS)
9	Berni Canani Roberto	2006	Therapeutic efficacy of butyrate in paediatric patients with congenital chloride diarrhoea
10	Boccuzzi Giuseppe	2007	New therapeutic approaches for anaplastic thyroid cancer: assessment of the benefit-risk profile of the combination valproic acid-paclitaxel
11	Bonini Stefano	2006	Multicentre, randomized, double masked, controlled clinical trial on the safety and efficacy of cyclosporine A eye drop treatment on patients with ocular cicatricial pemphigoid
12	Bonmassar Enzo	2007	Temozolomide in the chemo-immuno-therapy of refractory acute leukaemia of adult patients: the TRIAC protocol
13	Buzio Carlo	2007	Methotrexate as steroid-sparing agent in idiopathic retroperitoneal fibrosis: a multicentre randomized controlled trial
14	Calabrò Raffaele	2006	Arterial hypertension after successful aortic decoarctation: atenolol vs. enalapril comparison of efficacy and tolerability in paediatric age
15	Casali Paolo Giovanni	2005	Trabectedin (ET743) in metastatic or locally advanced myxoid/round cell liposarcoma pre-treated with chemotherapy

Appendix 1 *Continued*

No.	Principal Investigator	Call (Year)	Study title
16	Cavagnini Francesco	2007	Evaluation of the benefit-risk profile of retinoic acid in the treatment of Cushing's disease
17	Colao Annamaria	2005	Effectiveness and tolerability of treatment with cabergoline in Cushing's syndrome
18	Corchia Carlo	2006	Double blind randomized controlled study on the benefit-risk profile of the administration of Sildenafil (Viagra®) in the treatment of at term or late preterm newborn infants with severe respiratory disorders and pulmonary hypertension
19	Corradini Paolo	2005	Intensive chemo-immunotherapy as first-line treatment in adult patients with peripheral T-cell Lymphoma (PTCL)
20	De Santo Natale Gaspare	2005	Therapy of hyperhomocysteinemia in haemodialysis patients: effects of acetylcysteine and folates
21	Di Rocco Maja	2006	Multicentre randomized study to assess the efficacy and the safety of two therapeutic regimens(high dose of imiglucerase versus co-administration of imiglucerase and miglustat) in type I Gaucher disease patients who have not responded to previous treatment with low dose imiglucerase
22	Ensoli Barbara	2005	Phase II Trial for the Treatment of Advanced Classical Kaposi's Sarcoma with the HIV Protease Inhibitor Indinavir in Combination with Vinblastine/Bleomycin-based Chemotherapy
23	Fais Stefano	2005	Phase II clinical study on efficacy of proton pump inhibitors pre-treatment in osteosarcoma patients undergoing chemotherapy
24	Filla Alessandro	2005	Growth hormone in patients with amyotrophic lateral sclerosis as add-on therapy to Riluzole
25	Fiorilli Massimo	2006	Evaluation of the benefit/cost/safety profile of low-dose anti-CD20 monoclonal antibody (rituximab) treatment for refractory mixed cryoglobulinemia
26	Fraticelli Paolo	2006	Low-dose Oral Imatinib in the Treatment of Scleroderma Pulmonary Involvement: a Phase II pilot study
27	Gabrielli Armando	2005	Rare Diseases with microvascular involvement. High Dose Intravenous *N*-acetylcysteine versus Iloprost for early, rapidly progressive diffuse Systemic Sclerosis (Scleroderma)
28	Girardi Enrico	2007	Preventive therapy for multidrug-resistant tuberculosis: a multicentre clinical trial
29	Gringeri Alessandro	2007	Inhibitor development in previously untreated patients (pups) with severe haemophilia A when exposed to von Willebrand factor-containing plasma-derived factor VIII concentrates and to recombinant factor VIII concentrates: an international, multicentre, prospective, controlled, open label, randomized, clinical trial
30	Lambiase Alessandro	2005	Multicentre, randomized, double masked, controlled studies on the efficacy of Cyclosporine eye drop treatment in preventing Vernal Keratoconjunctivitis (VKC) relapses and in treating the acute phase
31	Locatelli Franco	2005	Use of anti-CD20 monoclonal antibody (rituximab) for the prevention and/or treatment of EBV-associated lymphoproliferative disease in recipients of haematopoietic stem cell and solid organ transplantation or in patients with primary immunodeficiency
32	Luisetti Maurizio	2007	Whole Lung Lavage Followed by Inhaled Sargramostin in the Treatment of Autoimmune Pulmonary Alveolar Proteinosis

Appendix 1 *Continued*

No.	Principal Investigator	Call (Year)	Study title
33	Marsico Serafino	2007	Randomized, single blind, controlled trial of inhaled glutathione versus placebo in patients with cystic fibrosis
34	Migliaresi Sergio	2007	Safety and clinical efficacy of abetimus sodium (LJP 394) in prevention of renal flares in patients with systemic lupus erythematosus and a history of renal disease
35	Morandi Lucia Ovidia	2007	Phase II, randomized double blind placebo-controlled study of tolerance and efficacy of salbutamol in adult patients with spinal muscular atrophy type III
36	Moretti Costanzo	2006	Multicentre, randomized, double masked, controlled study on efficacy and safety of bicalutamide treatment in patients affected by familiar polycystic ovary syndrome (PCOS)
37	Nobili Bruno	2005	A randomized, open-label therapeutic trial for the evaluation of the efficacy and safety of Neridronate (Nerixia) in the treatment of osteoporosis in patients with Thalassaemia Major and Severe Thalassaemia Intermedia
38	Novelli Giuseppe	2007	Study of efficacy of statins in association with bisphosphonates in Mandibuloacral Dysplasia and Hutchinson-Gilford Progeria Syndrome
39	Olivieri Attilio	2007	Imatinib Mesylate in the treatment of refractory extensive chronic Graft Versus Host Disease (cGVHD) with features Scleroderma-like
40	Palmieri Giovannella	2006	Phase II monitored clinical trial for evaluation of treatment of patients with Thymic Epithelial Tumours (TET) or Histiocytosis X (LCH) with Imatinib Mesylate
41	Parenti Giancarlo	2005	Evaluation of the efficacy of the treatment with ACE-inhibitors on the renal damage in patients affected by glycogen storage disease type 1a and type 1b and of the vitamin E on neutropenia of patients with glycogen storage disease 1b
42	Pareyson Davide	2005	Multicentre randomized double blind placebo controlled trial of long-term ascorbic acid treatment in Charcot-Marie-Tooth disease type 1a (CMT-trial: CMT-trial Italian with ascorbic acid long-term)
43	Parodi Oberdan	2006	Effects of tetrahydrobiopterin (BH4) on flow-mediated dilation in Cadasil patients: a randomized controlled trial
44	Pesci Alberto	2006	Hydroxychloroquine as Steroid-Sparing Agent in pulmonary Sarcoidosis (HySSAS). A multicentre, prospective, controlled, randomized trial
45	Pucci Neri	2006	Multicentre comparative randomized double blind cross over study with tacrolimus (FK506) 0·1% eyedrops and cyclosporine 1% eyedrops in children with severe active vernal keratoconjunctivitis, lasting 7 weeks, followed by an open trial lasting 24 months to evaluate long-term efficacy and safety of the treatment
46	Quaranta Luciano	2007	Efficacy and safety of topically applied prostaglandin analogue and carbonic anhydrase inhibitor for the treatment of paediatric glaucoma refractory to surgical procedures
47	Rambaldi Alessandro	2006	Randomized study comparing intravenous busulfan (i.v. bu; busilvex®) plus cyclophosphamide (bucy2) versus intravenous busulfan plus fludarabine (buflu) as conditioning regimens prior to allogenic haematopoietic stem cell transplantation in patients with acute myeloid leukaemia, chronic myeloid leukaemia and myelodysplastic syndrome
48	Redaelli Tiziana	2006	Evaluation of the tolerability and efficacy of erythropoietin (EPO) treatment in spinal shock: comparative study VS methylprednisolone
49	Ristori Giovanni	2007	Efficacy of riluzole in hereditary cerebellar ataxia: a randomized double-blind placebo-controlled trial

Appendix 1 *Continued*

No.	Principal Investigator	Call (Year)	Study title
50	Rossi Francesca	2007	A randomized multicentre, comparative, open label trial on efficacy and safety of treatment with endovenous anti-D immunoglobulin in comparison with endovenous immunoglobulin in children with chronic immune thrombocytopenic purpura
51	Ruperto Nicolino	2005	Phase II effectiveness randomized actively controlled clinical trial in new onset juvenile dermatomyositis: prednisone versus prednisone plus cyclosporine a versus prednisone plus methotrexate
52	Sansonno Domenico	2007	Use of sorafenib in the prevention of relapse of resected/ablated hepatocellular carcinoma in patients with hepatitis C virus chronic infection. a phase II randomized, controlled trial
53	Savelli Giordano	2007	Phase II A protocol for the treatment of patients affected by advanced stage Merkel cell tumours with 90Y-DOTATOC
54	Scarpa Maurizio	2006	Evaluation of the efficacy of enzyme replacement therapy in paediatric patients affected by mucopolysaccharidosis type II (Hunter syndrome)
55	Schena Francesco Paolo	2006	Multicentre, randomized, double blind, comparative clinical trial on the use of imatinib in association with angiotensin converting enzyme inhibitors and corticosteroids in the treatment of Ig-A nephropathy
56	Sorge Giovanni	2006	Evaluation of enzyme replacement therapy with Naglazyme (Aryplase) on joint disease in mucopolysaccharidosis type VI patients
57	Spada Anna Maria	2007	Treatment of hyperparathyroidism in patients with multiple endocrine neoplasia type 1 (MEN1) with the calcimimetic agent cinacalcet
58	Tagliavini Fabrizio	2005	A randomized, double-blind pilot study versus placebo for the evaluation of the efficacy of doxycycline administered by oral route in patients affected by Creutzfeldt-Jakob disease
59	Taroni Franco	2006	Randomized placebo-controlled double-blind trial to assess safety and efficacy of erythropoietin in adult patients with Friedreich's ataxia (pilot study)
60	Terzolo Massimo	2006	Efficacy of adjuvant mitotane treatment in prolonging disease-free survival in patients with adrenocortical carcinoma submitted to radical resection
61	Triggiani Massimo	2007	Study of the efficacy and tolerability of dasatinib in patients with systemic mastocytosis
62	Vannucchi Alessandro	2006	A phase 2 study of efficacy/safety of everolimus in subjects with idiopathic myelofibrosis (IMF)
63	Ventura Alessandro	2006	Randomized controlled double-blind vs. placebo multicentre study on the safety and effectiveness of thalidomide in the treatment of refractory Crohn's disease and ulcerative colitis in children and adolescents
64	Volterrani Maurizio	2005	Evaluation of tolerability and efficacy of the combination Sildenafil/Bosentan in patients with severe pulmonary hypertension

b) list of the 38 projects funded within the Area 2 (head-to-head comparison) of the three AIFA calls for proposal (2005–2007).

No.	Principal Investigator	Call (Year)	Study title
1	Amadori Dino	2006	Sequential treatment strategy for metastatic colorectal cancer: a phase III prospective randomized multicentre study of chemotherapy (CT) with or without bevacizumab as first-line therapy followed by two phase III randomized studies of CT alone or CT plus bevacizumab with or without cetuximab as second-line therapy

Appendix 1 *Continued*

No.	Principal Investigator	Call (Year)	Study title
2	Bucaneve Giampaolo	2007	Open, multicentre, randomized trial comparing two therapeutic approaches for the treatment of invasive fungal infections in neutropenic onco-haematologic patients. Empiric vs. 'presumptive' (preemptive) antifungal therapy
3	Cascinu Stefano	2006	Open-label randomized, parallel group, phase III, multicentre trial comparing two different sequences of therapy (irinotecan/cetuximab followed by FOLFOX-4 vs. FOLFOX-4 followed by irinotecan/cetuximab) in metastatic colorectal cancer patients treated with FOLFIRI/bevacizumab as first line chemotherapy
4	Cavallo Luciano	2007	Metformin vs. placebo in newly diagnosed type 1 diabetes mellitus: a randomized clinical trial
5	Ciccone Alfonso	2006	Synthesis: a randomized controlled trial on intra-arterial versus intravenous thrombolysis in acute ischaemic stroke
6	Citerio Giuseppe	2006	Anaesthesiological strategies in elective craniotomy: randomized, equivalence, open trial
7	Clavenna Antonio	2007	Efficacy of nebulized beclometasone versus placebo in preventing viral wheezing in pre-school children
8	Conte Pierfranco	2006	Short-HER: multicentre randomized phase III trial of adjuvant chemotherapy plus 3 months vs. 12 months of trastuzumab in breast cancer patients with HER2 positive disease
9	Corrado Antonio	2006	Long-term oxygen therapy (LTOT) in chronic obstructive pulmonary disease (COPD) patients with moderate chronic hypoxemia and chronic heart failure
10	Cucchiara Salvatore	2007	Multicentre comparative study between nutritional therapy alone and anti-TNF-alpha monoclonal antibody in inducing and maintaining remission in paediatric Crohn's disease: a randomized controlled trial
11	Del Mastro Lucia	2006	Efficacy and toxicity of trastuzumab at the maintaining dose of 1 mg/kg/week vs. the standard dose of 2 mg/kg/week in combination with chemotherapy in metastatic breast cancer patients. A phase III multicentre study
12	De Placido Sabino	2005	FATA – First Adjuvant Trial on AII aromatase inhibitors in early breast cancer. A phase 3 study comparing anastrozole, letrozole and exemestane, upfront (for 5 years) or sequentially (for 3 years after 2 years of tamoxifen), as adjuvant treatment of postmenopausal patients with endocrine-responsive breast cancer
13	Fabbri Leonardo M.	2005	Comparison of a serum procalcitonin (PRO-CT)-guided treatment plan with the standard guideline recommended antibiotic treatment plan for patients hospitalized with a diagnosis of exacerbation of COPD
14	Falcone Alfredo	2005	An open-label, multicentre, randomized phase III study of second-line chemotherapy with or without bevacizumab in metastatic colorectal cancer patients who have received first-line chemotherapy plus bevacizumab
15	Faldella Giacomo	2006	Efficacy and safety of continuous infusion of fentanyl for pain control in preterm newborns on mechanical ventilation
16	Gagliardi Luigi	2007	Treatment of hypotension in extremely preterm infants: a multicentre randomized controlled trial
17	Gasparini Giampietro	2006	A randomized translational phase III study: optimization of the FOLFIRI schedule in combination with bevacizumab for therapy of metastatic colorectal cancer, based on the genetic polimorphisms (pharmacogenetic evaluation) and analysis of circulating biomarkers. study coordinated by the CIPOMO association
18	Labianca Roberto	2005	A randomized trial investigating the role of FOLFOX-4 regimen duration (3 versus 6 months) and bevacizumab as adjuvant therapy for patients with stage II/III colon cancer

Appendix 1 *Continued*

No.	Principal Investigator	Call (Year)	Study title
19	Landoni Giovanni	2006	Cardiac protection by Sevoflurane in high risk patients undergoing cardiac surgery. A randomized controlled study
20	Mannucci Pier Mannuccio	2005	A randomized, controlled trial to evaluate the efficacy of low-molecular-weight heparin on pregnancy outcome of women with previous pregnancy complications
21	Massacesi Luca Milanese Clara	2005	Multicentre, randomized, controlled study of azathioprine versus interferon beta in relapsing-remitting multiple sclerosis
22	Mingardi Giulio	2006	A prospective, randomized, open label, blinded end-point (PROBE) trial to evaluate whether, at comparable blood pressure control, ACE inhibitor therapy more effectively than non ras inhibitor therapy reduces cardiovascular morbidity and mortality in chronic haemodialysis patients with left ventricular hypertrophy
23	Nicolucci Antonio	2005	A randomized, placebo-controlled study of the efficacy of low-dose aspirin in the prevention of cardiovascular events in subjects with diabetes mellitus treated with statins. (ACCEPT-D: Aspirin and simvastatin Combination for Cardiovascular Events Prevention Trial in Diabetes)
24	Perico Norberto	2005	A randomized, prospective, multicentre trial to compare the effect on chronic allograft nephropathy of mycophenolate mofetil versus azathioprine as the sole immunosuppressive therapy for kidney transplant recipients
25	Papi Alberto	2006	PRN budesonide/formoterol combination versus regular budesonide/formoterol combination plus PRN terbutaline in mild-moderate persistent asthma
26	Ravelli Angelo	2007	Comparison of the efficacy of intra-articular corticosteroid therapy administered alone or in combination with methotrexate in children with juvenile idiopathic arthritis: a phase II, randomized, actively controlled, multicentre trial
27	Remuzzi Giuseppe	2005	A randomized, prospective, open-label blinded end point (PROBE) trial to evaluate whether, at comparable blood pressure control, combined therapy with the ACE inhibitor benazepril and the angiotensin II receptor blocker (ARB) valsartan reduces progression to ESRD more effectively than benazepril or valsartan alone in high risk patients with type 2 diabetes and overt nephropathy (Valid study)
28	Riccardi Gabriele	2006	Effects of the addition of a thiazolidinedione as compared with a sulfonylurea on the incidence of macrovascular events in type 2 diabetic patients inadequately controlled with metformin
29	Roila Fausto	2007	Oral mucositis-induced pain during concomitant chemo-radiotherapy for head & neck cancer: randomized double blind trial to compare the effect of morphine mouthwashes versus placebo mouthwashes in reducing the use of systemic fentanyl or morphine therapy
30	Ruggenenti Piero	2005	A randomized, prospective, open-label blinded end point (PROBE) trial to evaluate whether, at comparable blood pressure control, combined therapy with the ACE inhibitor benazepril and the angiotensin II receptor blocker (ARB) valsartan, reduces the incidence of microalbuminuria more effectively than benazepril or valsartan alone in hypertensive patients with type 2 diabetes and high normal albuminuria (Variety study)
31	Santoro Armando	2005	Top trial: a randomized clinical trial of trastuzumab (herceptin®) optimization in patients with locally advanced and/or metastatic breast cancer overexpressing HER2 after a first-line chemotherapy plus trastuzumab

Appendix 1 *Continued*

No.	Principal Investigator	Call (Year)	Study title
32	Scanni Alberto	2006	Optimization of erlotinib for the treatment of patients with advanced non-small cell lung cancer: an Italian randomized trial
33	Strippoli Giovanni	2005	Cardio-renal effects of renin angiotensin system inhibition in cardio-renal risk patients: comparative randomized trial of angiotensin converting enzyme inhibitors, angiotensin receptor blockers or their combination in patients with one or more cardiovascular risk factors, screen positive for albuminuria or proteinuria, diabetic or not diabetic. the cardio-renal protection trial
34	Tognoni Gianni	2006	Effects of the dose of erythropoiesis stimulating agents on cardiac-cerebrovascular outcomes and quality of life in haemodialysis patients. The dose of Erythropoietins (DOSE) trial
35	Toni Danilo	2006	A randomized controlled trial of alteplase (RT-PA) vs. standard treatment in acute ischaemic hemispheric stroke in patients aged more than 80 years, where thrombolysis is initiated within 3 h after stroke onset
36	Utili Riccardo	2007	Randomized, open-label clinical trial on the efficacy of colistin plus rifampicin treatment versus colistin alone for severe infections by multidrug-resistant acinetobacter baumannii
37	Zanchetti Alberto	2005	PHIDIAS - Prevention of Hypertension Incidence and Diabetes Italian Assessment Study Therapeutic Strategies of Prevention of Diabetes and Hypertension in Subjects with Metabolic Syndrome and High-Normal Blood Pressure
38	Zappia Mario	2007	Levodopa Administration Modalities and Pramipexole in Parkinson's disease (LAMP-PD study). A multicentre, randomized, four parallel groups, active-controlled study to evaluate the risk of dyskinesia in early PD

c) list of the 49 projects funded within the Area 3 (pharmacovigilance and appropriateness) of the three AIFA calls for proposal (2005–2007).

No.	Principal Investigator	Call (Year)	Study title
1	Ammassari Adriana	2006	Prospective randomized controlled multi-dimensional trial on an informative and educational programme for the appropriate use on antiretroviral drugs focused on patients and patient associations: effect on adherence improvement
2	Barbui Corrado	2007	Effectiveness and tolerability of lithium in subjects with treatment-resistant depression and suicide risk: randomized, pragmatic, superiority trial
3	Bernardi Mauro	2006	The use of human albumin for the treatment of uncomplicated or refractory ascites in patients with liver cirrhosis: a randomized clinical trial
4	Bianchi Maria Luisa	2005	Improving adherence to the oral therapy of post-menopausal and senile osteoporosis with targeted interventions: a comparison between the standard method of medical prescription and two methods characterized by an increasing involvement of the patient
5	Biondi Zoccai Giuseppe	2007	Systematic review of controlled clinical trials on pharmacological treatments for acute nontubercolous pericarditis and its recurrences
6	Bonati Maurizio	2006	Prescription, efficacy, and safety of psychotropic drugs in the Italian paediatric population
7	Bortolus Renata	2006	Randomized clinical trial to evaluate the efficacy of high dose of folic acid to prevent the occurrence of congenital malformations

Appendix 1 *Continued*

No.	Principal Investigator	Call (Year)	Study title
8	Calabresi Paolo	2006	Sodium valproate in the treatment of medication overuse headache: a controlled randomized clinical trial
9	Caltagirone Carlo	2006	Mortality of elderly using conventional and non conventional antipsychotic drugs for the behavioural and psychological symptoms of dementia and for other psychical disorders
10	Caputi Achille Patrizio	2005	Effectiveness of computerized automatic reminders in improving pharmacological prescription in high-risk cardiovascular patients in primary care: a cluster-randomized controlled trial
11	Carta Mauro Giovanni	2005	The use of drugs for mood disorders in Italy
12	Caruso Domenico	2007	'Dieciannidivitainpiù' (a 10 years longer life): a therapeutic education programme for hypertensive patients
13	Cianciaruso Bruno	2007	Impact of antihypertensive therapy on mortality and cardiovascular events in haemodialysis patients: a systematic review
14	Craxì Antonio	2005	A multicentre observational study to evaluate factors influencing efficacy, tolerance and compliance to antiviral treatment with interferon and ribavirin in chronic hepatitis C patients in daily clinical practice
15	D'amico Roberto	2007	Efficacy, toxicity, duration and modalities of administration of anti-HER2 agents in HER-2 positive breast cancer: a prospective systematic review
16	Davoli Marina	2007	Cochrane systematic review to evaluate the efficacy, safety and cost effectiveness of Gamma-hydroxybutyric acid (GHB), acamprosate, benzodiazepines and anticonvulsants for the treatment of the Alcohol Withdrawal Syndrome (AWS)
17	Del Tacca Mario	2005	Safety and effectiveness of antidepressant treatments in general practice: an observational prospective study from the Pharmasearch network, with a Pharmacogenetic sub-study on cases of therapeutic drug failure and adverse drug reaction
18	Faggiano Fabrizio	2007	Nested case-control study to assess risk of overdose, AIDS and acute death in the VEdeTTE cohort of heroin addicts in the Piedmont and Lazio Regions in relation to being in or out of treatment, the length and type of therapy, and the time occurred from the interruption of treatment
19	Ferrara Nicola	2005	Evaluation of an educative/informative strategy on drugs use in elderly population with chronic-degenerative diseases in several care setting: a controlled randomized study
20	Ferrarese Carlo	2007	Comprehensive information imparted to patients with epilepsy and co-morbidity and decreased prevalence of adverse treatment effects
21	Ferratini Maurizio	2007	Effects of an e-learning intervention to improve suboptimal prescribing and reduce the incidence of adverse events in elderly nursing home residents
22	Floridia Marco	2007	The Italian National Programme on Surveillance on Antiretroviral Treatment in Pregnancy
23	Gambacorti Carlo	2005	Long-term effects of imatinib administration in chronic myeloid leukaemia patients
24	Gattinoni Luciano	2006	Efficacy of albumin administration for volume replacement in patients with severe sepsis or septic shock
25	Gerna Giuseppe	2007	Prevention of human cytomegalovirus (HCMV) mother-to-foetus transmission by administration of virus-specific hyperimune globulin to pregnant women with primary HCMV infection
26	Guidi Angelino	2005	Evaluation of a population-based multi-modal intervention to improve the quality of cancer pain analgesic treatment

Appendix 1 *Continued*

No.	Principal Investigator	Call (Year)	Study title
27	Lazzarin Adriano	2007	Randomized trial comparing immediate or deferred switch to a new HAART regimen in failing HIV infected patients: the role of lamivudine monotherapy. (MONO Study)
28	Maggiolo Franco	2007	LOTTI study (Long Term Treatment Interruptions) Strategic long-term, immunologically driven treatment interruptions in patients on effective HAART: a controlled, randomized study
29	Magrini Nicola	2005	Pharmacists' outreach visits and new information formats: cluster and single-doctor randomized controlled trials for evaluating their feasibility and impact on knowledge, attitudes and prescribing practices of General Practitioners in three Italian regions
30	Marchioli Roberto	2005	Rischio assoluto cardiovascolare – epidemiologia (RIACE)
31	Mazzaglia Giampiero	2006	Assessing the risk/benefit profile of bisphosphonates therapy in the secondary prevention of osteoporotic fractures: results from a retrospective cohort study with regional claims databases
32	Mezzalira Luigi	2005	Italian ISDB study on depression – ISD
33	Moroni Flavio	2007	Methadone dose adjustments, plasma R-methadone levels and therapeutic outcome of opioid addiction
34	Naldi Luigi	2005	Establishment of a European surveillance network to assess the long-term effectiveness and safety of biological agents, i.e. tumour necrosis factor alpha (TNF-alpha) antagonists and T-cell targeted molecules, in the treatment of psoriasis with particular attention to the risk of rare events
35	Panei Pietro	2005	Long-term safety of the drugs used in the treatment of school-aged children with attention deficit/hyperactivity disorder and epidemiology of the disease in the Italian population
36	Pani Pier Paolo	2007	Modafinil and cognitive behavioural treatment (CBT): a placebo-controlled double-blind multicentre trial in the treatment of cocaine dependence
37	Perucca Emilio	2005	A prospective study on long-term outcome and potential usefulness of an intervention aimed at reducing adverse effects in patients with refractory epilepsy
38	Pierannunzio Daniela	2006	Implementation and evaluation of a training programme on orphan drugs targeting patients' associations and families of patients with rare diseases
39	Pistelli Riccardo	2007	Efficacy of an educational programme on health outcomes in COPD patients with documented co-morbidities
40	Raschetti Roberto	2006	Alzheimer's Disease and antipsychotics: a long-term, multicentre, double blind, randomized clinical trial
41	Rizzetto Mario	2005	Study of the use in Italy in routine clinical practice of pegylated interferons for the therapy of chronic hepatitis C. proposed by the società italiana di gastroenterologia (SIGE), the istituto superiore di sanità (ISS), the associazione italiana dei gastroenterologi ospedalieri (AIGO), the associazione italiana studio fegato (AISF), the società italiana di malattie infettive e tropicali (SIMIT)
42	Samani Fabio	2005	Evaluation of prescribing pattern and safety profile of antidepressant and antipsychotic medications in Italian general practice
43	Scroccaro Giovanna	2005	Prophylactic prescription of low molecular weight heparin in the orthopaedic surgical setting: impact of regional guidelines
44	Tabolli Stefano	2005	Evaluation of the impact of writing exercises and educational interventions on quality of life, use of health resources, and adherence to treatment in patients with psoriasis
45	Todesco Silvano	2005	The risk/benefit profile of biologic agents in real-world rheumatology and dermatology practice

Appendix 1 *Continued*

No.	Principal Investigator	Call (Year)	Study title
46	Torri Valter	2007	A systematic review on the novel targeted therapies in the treatment of advanced non small cell lung cancer (NSCLC)
47	Trimarco Bruno	2005	Improvement of persistence and adherence to diuretic treatment as first choice for hypertension: a study of active pharmacovigilance and pharmacogenetics.
48	Viegi Giovanni	2005	Respiratory allergic diseases: monitoring study of GINA and ARIA guidelines (ARGA)
49	Zanetti Alessandro	2006	Persistence of anti-HBS antibody and of immunologic memory for hepatitis b surface antigen in two cohorts of children immunized with hexavalent vaccines: implications for policy and booster vaccination

