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CLINICAL TRIALS

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Adverse events and discomfort in studies on healthy subjects: the volunteer's perspective

A survey conducted by the German Association for Applied Human Pharmacology

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Abstract *Objective*: The various good clinical practice (GCP) guidelines do not define the volunteering subject as an active party. The present survey addresses the volunteer's perception of study-related inconvenience and risk and its impact on their decision to enrol.
Methods: The survey consisted of a questionnaire to be filled out voluntarily and anonymously by healthy subjects who volunteered for enrolment in human pharmacology studies and who had participated in at least one previous study. Twenty-five categorised multiple-choice questions covered previous study experience, motives for volunteering, perception of and compliance with study directives and restrictions, past experience with adverse events, impact of the study environment on perceived well-being and the nature of adverse events likely to discourage them from enrolment.
Results: Seven centres contributed by providing at least 30 (range 30–100) evaluable questionnaires. The database consists of a total of 440 healthy subjects (30.5% females, 69.5% males), from 18 to over 60 years of age. Two hundred and seven subjects (47.1%) were company employees and 233 (52.9%) were external volunteers. Eighty nine percent only participated in studies at one particular centre. Some 53.3% indicated financial motives, 27.8% 'contribution to an improvement of pharmacotherapy', 12.7% 'social responsibility', while 6.2% indicated other motives, mainly the opportunity of a free medical check-up. Thirteen subjects (3%) admitted to not answering correctly to the recruitment questions; this limited reliability is suspected to be even larger when the answer might preclude enrolment. From the volunteers' perspective, the environmental study conditions clearly appeared to have a highly relevant impact on their personal well-being. Some 17.1% of the subjects reported to have suffered adverse events occasionally and 2.7% frequently; but 14% admitted not reporting adverse events promptly and about 20% indicated that, with respect to previous adverse events, they first sought advice from other volunteers rather than from the investigator.
Conclusions: Adverse events and inconveniences are inherent to nontherapeutic studies in healthy subjects. From the volunteer's perspective it appears that the incidence of adverse experiences in such studies exceeds the reported frequencies from investigators considerably. This finding suggests that investigators are usually not aware or able to ascertain the true incidence of adverse events. The present survey also confirms that pertinent information on the personal history may be unreliable. Volunteers are reluctant to answer questions regarding, in particular, their smoking habits, caffeine and alcohol consumption. Regarding the matter of informed consent, a noteworthy contradiction between the volunteers' attitude and behaviour became apparent. Although the volunteers admit that even rather minor adverse events ordinarily would discourage them, they still consent to enrolment. In view of this apparent contradiction, there is no alternative to the investigator's personal responsibility to counsel and protect the subject. Surveys such as this one may contribute to the awareness that the explicitness of GCP guidelines merely define the format, but not the content quality of these fundamental ethical values, which remain the unique burden and challenge of the investigator.

Key words Adverse events, Healthy volunteers

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Introduction

The rights, safety and well-being (defined as physical and mental integrity) of the trial subjects are among the central motives of good clinical practice (GCP) [1, 2] and the ethical principles based on the Declaration of Helsinki. Volunteers participating in nontherapeutic trials are subject to inconveniences and risks, without any likely personal benefit other than a fair remuneration [3]. This lack of personal benefit needs to be balanced by the largest possible benefit for society [4] and the smallest possible individual risk and inconvenience [2], in healthy subjects in particular. The various legal and regulatory directives and guidelines explicitly and extensively define the responsibility and authority of the ethics committee, the investigator and the study sponsor in this regard. However, these regulations do not define the subject as an active party. Little is known about how the subjects perceive these issues themselves.

The AGAH (Arbeitsgemeinschaft für Angewandte Humanpharmakologie e.V., 'Association for Applied Human Pharmacology') is a German organisation of professionals in applied human pharmacology, working in the pharmaceutical industry, in contract research organisations (CROs) and in academia [5]. The working group on ethics, volunteer issues and adverse events ('Arbeitsgruppe Probanden, Ethik, unerwünschte Ereignisse') of the AGAH has conducted a survey amongst its members to address these aspects from the perspective of the volunteer subjects. The present paper summarises the main findings.

Methods

The members of the AGAH were invited to participate in a survey which consisted of a questionnaire to be filled out voluntarily and anonymously by healthy subjects who volunteered for enrolment in human pharmacology studies and who had participated in at least one previous study. All centres were professionally run by suitably qualified staff, who adhered to the principles of the Declaration of Helsinki, the notes of guidance of GCP and the local legal requirements for the orderly conduct of studies in volunteering subjects (the German drug law in particular). As such, a nonliability insurance cover is in place, about which the volunteers are informed in detail during the informed consent interview and in the respective consent forms. Twenty-five questions covered demographic aspects, previous study experience, motivation and reasons for volunteering, perception of and compliance with study directives and restrictions, previous experience with adverse events, impact of the study environment and conditions on perceived well-being during the study and the nature of adverse events likely to discourage them from enrolment. The questionnaire was originally written in German. For one centre, it was translated into Dutch by suitably qualified translators and cross-validated by investigators who were fluent in both languages. To most questions, the subject had to answer from a choice out of 3–4 predefined categorised options, including the possibility to answer in his/her own wording. For some questions, multiple answers were permitted. A copy of the questionnaire and the full analysis of the data can be requested from the authors.

Database

Six human pharmacology centres in Germany (centres A and C to G) and one in The Netherlands (centre B) contributed by providing at least 30 (range 30–100) evaluable questionnaires. Two centres (A and B) were CROs and five (C to G) were clinical research units within a pharmaceutical company. The participating centres are presented in detail at the end of this article. Although not all questions were answered by each subject, all questions could be retained for evaluation as they were answered by a sufficiently large fraction of the total group (i.e. >95% in 22 of 25 questions, minimum of 88.4% evaluable answers). Large quotas of missing answers were recorded only for questions regarding habitual consumption of caffeine (7.7%), nicotine (10.5%) and alcohol (11.4%). Percentages reported here generally refer to the complete database of 440 available questionnaires. Therefore, the quota of missing answers can be calculated for each question (100 minus the sum of percentages indicated for the respective question), even when it is not explicitly stated. The analysis is merely descriptive, using the study centre as main and sole stratum. Possible further strata, such as age, gender, occupation, previous study experience, country and internal versus external recruitment, are not equally distributed across the study centres and were not formally evaluated, as they are an inherent but indistinguishable part of the overall centre effects.

Results

Demographics

The database consists of a total of 440 healthy subjects (30.5% females, 69.5% males), from 18 to over 60 years of age. Two hundred and seven subjects (47.1%) were company employees and 233 (52.9%) were external volunteers. The current occupations of the latter were as follows: 75 were employed (32.2%), 68 were students (29.2%), 26 were unemployed (11.2%), 21 were retired (9.0%) and 19 were housewives (8.2%). The CROs almost exclusively recruited volunteers externally. Centres within companies recruited either mainly externally (centre C), internally (centres D, F and G) or both (centre E). Further details are specified in Table 1.

Previous study experience

All volunteers had previously participated in at least one human pharmacology study. The majority of subjects (73.9%) had taken part in several studies over many years and the largest proportion had participated in two to five studies (44.3%). A total of 51.6% had previously taken part in more than one study per year.

Interrelationship of study participants and centres

Most subjects (89.0%) only participated in studies at one particular centre. Forty-five subjects (10.2%) stated previous experience with more than one centre. At the time of the interview, 13 subjects (2.9%) were listed in the active-volunteers register of more than one centre. While 12 subjects (2.7%) had considered enrolment in

Table 1 Demography

Question	Answers	Centres							Total (*n*)	Total (%)
		A	B	C	D	E	F	G		
Number of subjects		100	30	59	40	87	60	64	440	
Gender	Female	28	30	11	2	23	28	12	134	30.5
	Male	72	0	48	38	64	32	52	306	69.5
Age (years)	18–25	15	16	5	1	9	5	7	58	13.2
	26–35	46	6	30	10	63	26	25	206	46.8
	36–45	21	0	8	20	14	27	27	117	26.6
	46–60	2	8	5	6	0	0	4	25	5.7
	>60	16	0	11	3	1	0	0	31	7.1
	No answer	0	0	0	0	0	2	1	3	0.7
Recruitment	Internal (company employees)	4	1	6	37	37	59	63	207	47.1
	External	96	29	53	3	50	1	1	233	52.9
Current occupation (external volunteers only)	Student	19	17	15	0	17	0	0	68	29.2
	Employed	23	6	18	0	28	0	0	75	32.2
	Housewife/-man	10	6	2	0	1	0	0	19	8.2
	Unemployed	18	0	7	0	1	0	0	26	11.2
	Retired	8	0	9	3	1	0	0	21	9.0
	Others	18	0	2	0	2	1	1	24	10.3

two studies less than 2 months apart, only four of them (0.9%) finally participated in both trials. Further details are listed in Table 2.

Main motives for volunteering

Since it was permitted to name several reasons for volunteering, multiple answers (a total of 629) were given: 335 subjects (53.3% of all answers and 76% of all subjects) indicated financial motives; 175 (27.8% of all answers and 40% of all subjects) indicated 'contribution to an improvement of pharmacotherapy'; 80 (12.7% of all answers and 18% of all subjects) indicated 'social responsibility'; and 39 (6.2% of all answers and 9% of all subjects) specified other motives, mainly the opportunity for a free medical check-up. Financial motives were definitely the main reason for volunteering: in more than or equal to 80% of all subjects in centres A, B, E, F and G and in 50 and 56% in centres D and C, respectively.

Reliability of answers to eligibility questions

Thirteen subjects (3%) admitted to not answering correctly to the recruitment questions regarding their medical history (including lifestyle, concomitant medication, use of social drugs etc.): six by mistake, six because they did not expect this to result in a relevant risk and one because he wanted to be sure of getting enrolled.

Impact of pre-study information

Twenty-two percent of the volunteers judged that the study information provided on enrolment was likely to

Table 2 Study history

Question	Number of answers	Centres							Total (*n*)	Total (%)
		A	B	C	D	E	F	G		
Number of years as volunteer	<1	54	17	8	0	8	2	22	111	25.3
	1–3	34	12	34	7	64	13	8	172	39.2
	4–6	10	1	14	12	13	17	8	75	17.1
	7–10	1	0	1	10	1	14	8	35	8.0
	>10	1	0	1	11	1	14	18	46	10.5
	No answer	0	0	1	0	0	0	0	1	0.2
Number of past studies	1	40	14	9	1	17	5	22	108	24.6
	2–5	44	16	33	13	56	20	13	195	44.3
	6–10	10	0	14	10	8	19	6	67	15.2
	>10	6	0	3	16	0	16	22	63	14.3
	No answer	0	0	0	0	6	0	1	7	1.6
Past enrolment in more than 1 study per year	No	48	19	28	6	46	30	32	209	47.5
	Yes	52	10	31	34	40	30	30	227	51.6

affect their perception and awareness of eventual adverse events: 64% were certain that this had no effect, whereas 13% found this difficult to assess.

Ability to notice and express changes of body function as possible adverse events

Most subjects (75–93%, depending on the study centre) believed that they were able to perceive and communicate changes in their general well-being. Most of the remaining subjects (5–20%) were certain of being able to perceive such changes, but found it difficult to verbalise them.

Personal lifestyle and impact of study restrictions and directives

Subjects participating in human pharmacology studies are usually instructed to abstain from xanthines, alcohol and smoking. They are, furthermore, subjected to an often unusual and strenuous time schedule or may have to accept strictly standardised meals. The subjects were asked about their consumption habits with regard to caffeine, nicotine and alcohol and whether they believed that restrictions of those substances might have had a negative impact on their well-being in previous studies.

Most subjects (57.1%) reported that they drink coffee and/or tea regularly; only 14.3% indicated hardly or ever consuming xanthine containing beverages. Of all subjects, 7.7% gave no information of their caffeine consumption. However, such restrictions were not viewed as a source of eventual discomfort (46.1%, not at all; 39.3%, only marginally).

Most subjects (59.1%) stated that they were non-smokers, while 1.36% smoked occasionally. Although 29.1% smoked regularly, only 8.2% answered that smoking restrictions might have had a marked negative impact on their well-being, and 10.5% of the volunteers refused information on their smoking status.

While only 7.3% of the volunteers stated that they drink alcoholic beverages regularly, the majority of subjects (44.1%) indicated only occasional alcohol consumption. Further 29.8% and 7.5% respectively, answered that they hardly or never drink alcohol, and 11.4% made no statements about their drinking habits. Abstinence from alcoholic beverages was not expected to affect well-being (80.9%, not at all; 16.6%, only mildly).

About 10% judged that the unusual and strenuous time schedule was distressing (8.4%, markedly; 1.6%, substantially). The study diet was also not experienced as a relevant source of discomfort (91.6%, not at all or only slightly). Further details are given in Table 3.

Impact of study environment/general study conditions

The subjects were asked whether they expected that the study environment could have an impact (whether positive or negative) on their well-being. Details are listed in Table 3. It should be noted that, from the perspective of the volunteers, the environmental study conditions appeared to have the most relevant impact on their personal well-being (either positive or negative): study rooms and infrastructure (30.9% expect moderate to substantial impact), behaviour and action of the study staff (24.8%), monotony (24.5%), meals (23.9%), blood sampling (18.9%) and the inter-relationship with other volunteers (18.6%).

Table 3 Environmental conditions perceived to have relevant impact on general well-being. Percentage of subjects per centre who expect and/or previously experienced a moderate to substantial impact of the study environment on their well-being (referred to the complete database of 440 questionnaires)

Specific study condition	Centres							Total
	A	B	C	D	E	F	G	
Restrictions with regard to xanthines	17.0	3.3	3.4	17.5	18.4	13.3	10.9	13.2
Restrictions with regard to alcohol	4.0	0.0	0.0	2.5	3.5	0.0	0.0	1.8
Restrictions with regard to nicotine	12.0	6.7	1.7	12.5	3.5	11.7	9.4	8.2
Restrained time schedule	8.0	20.0	6.8	5.0	17.2	8.3	6.3	10.0
Dietary restrictions and standardisation	13.0	0.0	20.3	10.0	2.3	5.0	0.0	7.7
Lack of autodetermination (heteronomy)	12.0	10.0	15.3	7.5	6.9	6.7	0.0	8.4
Other volunteers	23.0	3.3	33.9	10.0	23.0	18.3	4.7	18.6
Study staff and personnel	27.0	16.7	32.2	30.0	27.6	20.0	15.6	24.8
Study rooms and infrastructure	36.0	16.7	42.4	25.0	28.7	33.3	23.4	30.9
Monitoring and surveillance	10.0	3.3	22.0	12.5	20.7	16.7	9.4	14.3
Meals	35.0	6.7	27.1	32.5	17.2	20.0	18.8	23.9
Confined bed rest	16.0	13.3	23.7	30.0	20.7	16.7	4.7	17.5
Monotony	24.0	10.0	37.3	20.0	25.3	23.3	23.4	24.5
Changes of day rhythm	19.0	13.3	15.3	20.0	29.9	8.3	12.5	18.0
Medical methods and techniques (ECG, blood pressure etc.)	5.0	6.7	8.5	7.5	9.2	13.3	6.3	8.0
Blood sampling	20.0	23.3	11.9	15.0	23.0	18.3	18.8	18.9

General expectations of adverse events

Some 34.6% of the volunteers thought that the incidence of adverse events in human pharmacology studies was likely to be overestimated; 8.9% expected it to be underestimated. Most subjects (52.5%) had no opinion in this regard.

Previous experience with adverse events

Four hundred and thirty-three subjects provided evaluable answers with regard to previous study experience. The reported incidences of previous adverse events were as follows: 31.0% never; 47.7% rarely; 17.1% occasionally; and 2.7% frequently. The most prominent previous adverse experiences were headache and fatigue with incidences of about 27.5% and 15.0%, respectively. The likelihood of a positive response is evidently larger in subjects with longer previous study experience. A substantial fraction of the subjects in centres A, B and G had participated in only one previous study. The relative proportion of subjects who had no past experience with adverse events was as follows: 37, 50, 44, 10, 33, 7 and 38%, in centres A, B, C, D, E, F and G, respectively.

Of those subjects who stated to have suffered adverse events in the past, 14.3% stated that they did not report them promptly, 20.3% first sought advice from other volunteers, 63.0% informed the medical staff without delay, while about 1% consulted their family physician.

Sixteen subjects (3.6%) had considered withdrawing during the course of a previous study because of adverse events; 10 (2.3%) nevertheless changed their mind subsequently. Twenty-eight subjects (6.4%) had indeed discontinued a previous study prematurely, either on their own initiative because of clinically evident subjective adverse events ($n = 10$, 2.3%) or – more frequently – on the initiative of the clinical investigator ($n = 18$, 4.1%). In the majority of cases, the investigator's decision to withdraw a subject prematurely from a study appeared to be the result of deviations of objective clinical parameters which were not perceptible by the subjects (e.g. laboratory or ECG parameters).

Most subjects (68.8%) had the impression that the investigator and/or his staff always reacted appropriately to adverse events reported, 10.6% felt that this was not always the case, and 19.2% found it difficult to judge.

Adverse events discouraging from enrolment

Finally, the subjects were asked to review a list of signs and symptoms and to indicate whether they would be willing (''yes''; ''probably yes''; ''probably no''; ''no'') to participate in a study in which they might suffer – albeit transiently – a given symptom. The outcome is summarised in Table 4, which details the percentage of subjects discouraged from enrolling (i.e. those answering ''probably no'' or ''no'') when a given symptom was to be expected. Tiredness and fatigue and even exhaustion were only slightly discouraging. In contrast, the expectation of vomiting (63.1%), migraine (67.0%), visual disturbance (66.7%), change in libido and potency (67.9%) or hair loss (87.2%) were clearly discouraging subjects considering participation.

Discussion

Several guidelines and directives stipulate the responsibility of the ethics committee, the investigator and the sponsor to ensure the rights, safety and well-being of the trial subjects. These regulations do not define the subject as an active party, though, and little is known about how healthy subjects perceive these issues.

Table 4 Discouraging events. Percentage of subjects per centre who claim probably or definitely not to enrol in a study when a given sign or symptom were likely to occur (albeit transiently); values refer to the complete database of 440 questionnaires

Sign of symptom	Centres							Total
	A	B	C	D	E	F	G	
Tiredness/fatigue	2.0	40.0	3.4	0.0	4.6	0.0	0.0	1.8
Exhaustion	9.0	80.0	5.1	0.0	4.6	0.0	3.1	9.5
Nausea	50.0	66.7	28.8	22.5	48.3	10.0	31.3	37.3
Vomiting	68.0	80.0	57.6	40.0	74.7	35.0	60.9	60.7
Stomach-ache	59.0	63.3	50.8	32.5	57.5	48.3	51.6	53.0
Diarrhoea	57.0	66.7	50.8	32.5	57.5	38.3	37.5	49.3
Weight gain	44.0	60.0	47.4	12.5	41.4	53.3	34.4	42.0
Headache	33.0	56.7	23.7	12.5	46.0	20.0	21.9	30.7
Vertigo	38.0	70.0	28.8	10.0	49.4	16.7	26.6	34.1
Migraine	68.0	90.0	57.6	45.0	72.4	58.3	57.8	64.1
Visual disturbances	62.0	90.0	64.4	50.0	77.0	55.0	53.1	63.9
Smell disturbances	43.0	63.3	33.9	20.0	32.2	28.3	28.1	34.8
Taste disturbances	41.0	60.0	32.2	15.0	31.0	21.7	29.7	32.5
Sexual dysfunction (change of libido/potency)	62.0	63.3	67.8	57.5	63.2	71.7	71.9	65.5
Hair loss	78.0	86.7	83.1	87.5	85.1	85.0	87.5	83.9

In nontherapeutic studies, the central issue is that the subject is exposed to inconveniences and risk without any personal benefit other than a fair remuneration. Subjects participating in human pharmacology studies must consent of their own free will to this after having been comprehensively informed. The process of informed consent is explicitly and extensively specified in most regulations. It implies that the subjects are to be informed of all aspects of the trial that are relevant to their decision to participate, that they are capable of understanding this information and that their free will to accept possible risks is not compromised or influenced by social or professional pressure ('vulnerable' subjects [2]) or substantial financial need.

Information on the personality structure of volunteers is scarce but there are indications of a relatively high extrovertism [6]. Meticulous investigations in student volunteers also confirm that volunteers tend to be more extrovert, flexible, tolerant or less impulsive, more self-confident and are more satisfied and optimistic than the general norm; they also have lower levels of state and trait anxiety and are more sensation, thrill and adventure seeking than the student norm [7]. In contrast, other surveys indicate that volunteers tend to be substantially balanced, self-assured, reliable and motivated by extremely realistic objectives [8]. Financial compensation, nevertheless, is likely to be the prime motive of study candidates, especially in the younger volunteers and/or in subjects who are not company employees of the pharmaceutical industry or CROs (i.e. external volunteers). Older persons, in contrast, might also be motivated by the opportunity of getting a free medical check-up [9]. The present survey confirms this, but also stresses the importance of ethical ('contribution to an improvement of pharmacotherapy') and social ('social responsibility') motives of ancillary importance, especially when company employees are enrolled. Although these social motives may be reassuring, there is no reason not to accept financial motives as legitimate. Indeed, neither the sponsor nor the investigator are likely to base their interest on merely social motives. The remuneration of the subjects needs to be fair and appropriate though [3] and the amount and method of payment ought to be subject to ethical review in order to ensure that it may not be suspected as coercion or undue influence.

In return for a fair remuneration, the subject accepts being exposed to discomfort or distress from the study restrictions, constraints and methods. The present inquiry suggests that the subjects do not usually consider the restrictions with regard to xanthines, nicotine or diet to have a negative impact on their well-being; in general, only 10–13% considered this to be an issue in the present survey. This seems even less with regard to alcohol (see Table 3). It is to be stressed, though, that volunteers frequently provide inaccurate information concerning their lifestyle, as this might exclude them from study enrolment and the monetary incentive [10]. The number of smokers, for instance, who enter clinical trials designed for non-smokers may be greater than 25%, when the subjects are selected on the basis of their own statements rather than objective measures of nicotine exposure [11]. The present survey seems to confirm the observation that pertinent information on the personal history is frequently under-reported and possibly falsified by the fact that 10.5% and 11.4% of all subjects, respectively, did not answer the questions regarding their smoking habits and alcohol consumption. These numbers are particularly noteworthy, since the completion of the questionnaire was voluntary and anonymous and, thus, the information given could not have been suspected to be connected with probable disadvantages regarding future study participation. This issue is relevant since withdrawal syndromes after cessation of alcohol, nicotine or even caffeine [12] might be an underestimated source of 'background noise' in the evaluation of adverse drug reactions.

However, from the perspective of the volunteers, the environmental study conditions clearly appeared to have a more relevant impact on their personal well-being: study rooms and infrastructure (30.9% expect moderate to substantial impact), behaviour of the study staff (24.8%), monotony (24.5%), meals (23.9%), blood sampling (18.9%) and the interrelationship with other volunteers (18.6%). This finding is of special relevance as all centres participating in this survey have modern study facilities with a well-conceived infrastructure.

An open dialogue with volunteers in this regard may help to identify relevant issues. Social care or occupational programs by specially trained staff members could be offered to reduce this discomfort, especially for studies with in-house confinement over longer periods of time.

Furthermore, the subjects are exposed to the risk of eventual adverse drug reactions. The reported incidences of adverse drug reactions in studies on healthy subjects are low [13–18], especially if compared with the disturbances of well-being that can be related to the study environment/conditions, changes of lifestyle and the incidence of events under placebo (i.e. adverse non-drug reactions) [19, 20]. Older reports of very low incidences are likely to have been confined to severe events [13, 17]. More recently, investigators reported that about 4–7% of the healthy subjects under their care suffered minor events and 0.1–0.6% severe, potentially life-threatening events [15, 18]. The present survey clearly indicates higher incidences: 17.1% of the subjects reported having suffered adverse events occasionally and 2.7% frequently. There is no evident explanation for this difference, but it cannot be excluded that investigators are usually not aware or able to ascertain the true incidence of adverse events occurring in the course of studies with healthy volunteers. This suggestion is confirmed by the finding that about 14% of the subjects admitted not reporting adverse events promptly and about 20% would have first sought advice from other volunteers rather than the investigator. It must be emphasised that only about two thirds (63%) of all volunteers are likely to inform the medical staff without delay and/or reser-

vation. This confirms the general awareness of the investigators participating in the present survey that there is no justification to consider 'that the risk of participation in nontherapeutic research may not be greater than that of everyday life' [13]. This is especially true as there is always a risk – however small – of catastrophic events [21–23], even when precipitated by concomitant factors, of which the subject chose not to inform the investigator [21, 22]. It must be noted from the present survey that a small fraction of the subjects (3%) admitted to not answering correctly to recruitment questions regarding lifestyle, concomitant medication, use of social drugs etc. Although this may happen frequently by mistake, six subjects (1.4%) admitted that they did not expect that inaccurate information on their medical history may result in a relevant risk and one subject declared that he did so out of fear of not being enrolled.

Subjects need to be informed of the ''reasonably foreseeable'' risks and inconveniences [2]. As the extent of previous drug exposure is small in the early stages of a development program, the potential prominence (severity and incidence) of adverse events is difficult to estimate. As a rule, with new chemical entities, the unexpected is not unlikely to happen and the unforeseeable should be expected. In the late stages of the programme, especially in bioequivalence studies on already marketed drugs, the list of possible adverse reactions (derived from patient experience) might be so overwhelmingly long that any estimate of their foreseeable prominence in healthy subjects is likely to be quite confusing.

In conclusion, the present survey indicates that adverse events and inconveniences are inherent to nontherapeutic studies in healthy subjects. From the volunteer's perspective it appears that the incidence of adverse experiences in such studies considerably exceeds the frequencies reported by investigators. This finding suggests that investigators are usually not aware of, or able to ascertain, the true incidence of adverse events. The present survey also confirms that pertinent information on the personal history may be unreliable. Volunteers are, in particular, reluctant to answer questions regarding their smoking habits, caffeine and alcohol consumption.

With regard to the matter of informed consent, a noteworthy contradiction between the volunteers attitude and behaviour became apparent from the present survey: although the volunteers admit that even rather minor adverse events ordinarily would discourage them, they still consent to enrolment. There is no alternative to the investigator's personal responsibility to counsel and protect the subject in view of this apparent contradiction. Surveys such as this may contribute to the awareness that the explicitness of GCP guidelines merely define the format but not the content quality of these fundamental ethical values, which remain the unique burden and challenge of the investigator.

Appendix: Centres and contributors

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